L Number	Hits	Search Text	DB	Time stamp
1	6678	chimer$3 adj (antibody or immunoglobulin$1)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:18
2	7246	(single adj chain) adj (antibody or immunoglobulin$1)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:09
3	5834	Humaniz$5 adj (antibody or immunoglobulin$1)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:09
4	2641	scFv or sFv	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:10
5	12039	(chimer$3 adj (antibody or immunoglobulin$1)) or ((single adj chain) adj (antibody or immunoglobulin$1)) or (Humaniz$5 adj (antibody or immunoglobulin$1)) or (scFv or sFv)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:10
6	9003	CD4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:16
7	0	CD adj (scFv or sFv)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:11
8	430	OKT4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:11
9	0	OKT adj (scFv or sFv)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:12
10	99	Leu3a	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:12
11	225	Leu adj 3a	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:12
12	9228	CD4 or (CD adj (scFv or sFv)) or OKT4 or (OKT adj (scFv or sFv)) or Leu3a or (Leu adj 3a)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:13
13	101	((chimer$3 adj (antibody or immunoglobulin$1)) or ((single adj chain) adj (antibody or immunoglobulin$1)) or (Humaniz$5 adj (antibody or immunoglobulin$1)) or (scFv or sFv)) with (CD4 or (CD adj (scFv or sFv)) or OKT4 or (OKT adj (scFv or sFv)) or Leu3a or (Leu adj 3a))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:14
14	2802	cell adj separation	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:43
15	5	(((chimer$3 adj (antibody or immunoglobulin$1)) or ((single adj chain) adj (antibody or immunoglobulin$1)) or (Humaniz$5 adj (antibody or immunoglobulin$1)) or (scFv or sFv)) with (CD4 or (CD adj (scFv or sFv)) or OKT4 or (OKT adj (scFv or sFv)) or Leu3a or (Leu adj 3a))) and (cell adj separation)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:14

16	1740	anti adj CD4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:17
17	9	anti adj OKT4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:17
18	22	anti adj Leu3a	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:17
19	84	anti adj Leu adj 3a	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:18
20	1816	(anti adj CD4) or (anti adj OKT4) or (anti adj Leu3a) or (anti adj Leu adj 3a)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:18
21	33371	chimer$3 or (single adj chain) or humaniz$5 or scFv or sFv	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:20
22	105	((anti adj CD4) or (anti adj OKT4) or (anti adj Leu3a) or (anti adj Leu adj 3a)) with (chimer$3 or (single adj chain) or humaniz$5 or scFv or sFv)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:20
23	11	(((anti adj CD4) or (anti adj OKT4) or (anti adj Leu3a) or (anti adj Leu adj 3a)) with (chimer$3 or (single adj chain) or humaniz$5 or scFv or sFv)) and (cell adj separation)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:21
24	14	((((chimer$3 adj (antibody or immunoglobulin$1)) or ((single adj chain) adj (antibody or immunoglobulin$1)) or (Humaniz$5 adj (antibody or immunoglobulin$1)) or (scFv or sFv)) with (CD4 or (CD adj (scFv or sFv)) or OKT4 or (OKT adj (scFv or sFv)) or Leu3a or (Leu adj 3a))) and (cell adj separation)) or ((((anti adj CD4) or (anti adj OKT4) or (anti adj Leu3a) or (anti adj Leu adj 3a)) with (chimer$3 or (single adj chain) or humaniz$5 or scFv or sFv)) and (cell adj separation))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:39
25	820	(435/7.24).CCLS.	USPAT; US-PGPUB; EPO; DERWENT	2003/02/10 10:40
26	226	(435/372.3).CCLS.	USPAT; US-PGPUB; EPO; DERWENT	2003/02/10 10:40
27	479	(424/133.1).CCLS.	USPAT; US-PGPUB; EPO; DERWENT	2003/02/10 10:40
28	111	(424/135.1).CCLS.	USPAT; US-PGPUB; EPO; DERWENT	2003/02/10 10:40
29	102	(424/140.1).CCLS.	USPAT; US-PGPUB; EPO; DERWENT	2003/02/10 10:40
30	1005	(530/387.3).CCLS.	USPAT; US-PGPUB; EPO; DERWENT	2003/02/10 10:41

31	682	(530/391.1).CCLS.	USPAT; US-PGPUB; EPO; DERWENT	2003/02/10 10:41
32	2846	((435/7.24).CCLS.) or ((435/372.3).CCLS.) or ((424/133.1).CCLS.) or ((424/135.1).CCLS.) or ((424/140.1).CCLS.) or ((530/387.3).CCLS.) or ((530/391.1).CCLS.)	USPAT; US-PGPUB; EPO; DERWENT	2003/02/10 10:42
33	820	(CD4 or (CD adj (scFv or sFv)) or OKT4 or (OKT adj (scFv or sFv)) or Leu3a or (Leu adj 3a)) and (((435/7.24).CCLS.) or ((435/372.3).CCLS.) or ((424/133.1).CCLS.) or ((424/135.1).CCLS.) or ((424/140.1).CCLS.) or ((530/387.3).CCLS.) or ((530/391.1).CCLS.))	USPAT; US-PGPUB; EPO; DERWENT	2003/02/10 10:43
34	3745	cell adj (depletion or separation)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:44
35	3745	cell adj (depletion or separation)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:45
36	121	((CD4 or (CD adj (scFv or sFv)) or OKT4 or (OKT adj (scFv or sFv)) or Leu3a or (Leu adj 3a)) and (((435/7.24).CCLS.) or ((435/372.3).CCLS.) or ((424/133.1).CCLS.) or ((424/135.1).CCLS.) or ((424/140.1).CCLS.) or ((530/387.3).CCLS.) or ((530/391.1).CCLS.))) and (cell adj (depletion or separation))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/10 10:46

701,001
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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

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60
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NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 26	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 27	Oct 21	EVENTLINE has been reloaded
NEWS 28	Oct 24	BEILSTEIN adds new search fields
NEWS 29	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 30	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 31	Nov 18	DKILIT has been renamed APOLLIT
NEWS 32	Nov 25	More calculated properties added to REGISTRY
NEWS 33	Dec 02	TIBKAT will be removed from STN
NEWS 34	Dec 04	CSA files on STN
NEWS 35	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 36	Dec 17	TOXCENTER enhanced with additional content
NEWS 37	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 38	Dec 30	ISMEC no longer available
NEWS 39	Jan 13	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 40	Jan 21	NUTRACEUT offering one free connect hour in February 2003
NEWS 41	Jan 21	PHARMAML offering one free connect hour in February 2003
NEWS 42	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC

NEWS EXPRESS January 6 CURRENT WINDOWS VERSION IS V6.01a,
CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),

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                AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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FILE 'HOME' ENTERED AT 14:21:24 ON 10 FEB 2003

=> file ca
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                                                       ENTRY    SESSION
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FILE COVERS 1907 - 6 Feb 2003 VOL 138 ISS 7
FILE LAST UPDATED: 6 Feb 2003  (20030206/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s chimeric
         32258 CHIMERIC
            23 CHIMERICS
L1       32266 CHIMERIC
                (CHIMERIC OR CHIMERICS)

=> s humanized
L2        3037 HUMANIZED

=> s single(W)chain
        986061 SINGLE
          2445 SINGLES
        988166 SINGLE
```

```
                (SINGLE OR SINGLES)
        519493 CHAIN
        258588 CHAINS
        670874 CHAIN
                (CHAIN OR CHAINS)
L3        8450 SINGLE(W)CHAIN

=> s antibody or immunoglobulin!
        237080 ANTIBODY
        260498 ANTIBODIES
        358773 ANTIBODY
                (ANTIBODY OR ANTIBODIES)
         80904 IMMUNOGLOBULIN!
L4      396541 ANTIBODY OR IMMUNOGLOBULIN!

=> s cd4
L5       33999 CD4

=> s okt4!
L6         119 OKT4!

=> del l4-l6
DELETE L4-L6? (Y)/N:y

=> s antibody or immunoglobulin
        237080 ANTIBODY
        260498 ANTIBODIES
        358773 ANTIBODY
                (ANTIBODY OR ANTIBODIES)
         27983 IMMUNOGLOBULIN
         80899 IMMUNOGLOBULINS
         91448 IMMUNOGLOBULIN
                (IMMUNOGLOBULIN OR IMMUNOGLOBULINS)
         44756 IG
         12199 IGS
         50459 IG
                (IG OR IGS)
        110752 IMMUNOGLOBULIN
                (IMMUNOGLOBULIN OR IG)
L4      414793 ANTIBODY OR IMMUNOGLOBULIN

=> s CD4
L5       33999 CD4

=> s OKT4#
L6         435 OKT4#

=> s OKT(W)4#
           223 OKT
             1 OKTS
           224 OKT
                (OKT OR OKTS)
TERM '4#' EXCEEDED TRUNCATION LIMITS - SEARCH ENDED
You have entered a truncated stem which occurs in too many terms.
Make the stem longer and try again.  For example, if your original
term was 'degr?' to search for variations and the abbreviation for
'degradation', you could replace it with the expression '(degrdn OR
degrad?)'.  If your search term was numeric, e.g., 'C>5', reduce the
size of the range.

=> s leu3a
L7          96 LEU3A

=> s leu(W)3a
```

```
         31248 LEU
            52 LEUS
           282 LEI
           357 LEIS
         31927 LEU
                 (LEU OR LEUS OR LEI OR LEIS)
         19821 3A
L8         101 LEU(W)3A

=> s okt(W)4
           223 OKT
             1 OKTS
           224 OKT
                 (OKT OR OKTS)
       4509734 4
L9          24 OKT(W)4

=> s cd(W)4
        216875 CD
         25294 CDS
        236318 CD
                 (CD OR CDS)
       4509734 4
L10        731 CD(W)4

=> s l5 or l6 or l7 or l8 or l9 or l10
L11      34980 L5 OR L6 OR L7 OR L8 OR L9 OR L10

=> s anti(W)l11
        280670 ANTI
             7 ANTIS
        280676 ANTI
                 (ANTI OR ANTIS)
L12       1412 ANTI(W)L11

=> d his

     (FILE 'HOME' ENTERED AT 14:21:24 ON 10 FEB 2003)

     FILE 'CA' ENTERED AT 14:21:33 ON 10 FEB 2003
L1         32266 S CHIMERIC
L2          3037 S HUMANIZED
L3          8450 S SINGLE(W)CHAIN
L4        414793 S ANTIBODY OR IMMUNOGLOBULIN
L5         33999 S CD4
L6           435 S OKT4#
L7            96 S LEU3A
L8           101 S LEU(W)3A
L9            24 S OKT(W)4
L10          731 S CD(W)4
L11        34980 S L5 OR L6 OR L7 OR L8 OR L9 OR L10
L12         1412 S ANTI(W)L11

=> l1 or l2 or l3
L1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l1 or l2 or l3
L13      41620 L1 OR L2 OR L3

=> s l13(W)l4
L14       2787 L13(W)L4
```

```
=> s l14(5a)l11
L15         48 L14(5A)L11

=> s l13(W)l12
L16         30 L13(W)L12

=> s l15 or l16
L17         66 L15 OR L16

=> save temp
ENTER L#, L# RANGE, ALL, OR (END):l17
ENTER NAME OR (END):chimeric/a
ANSWER SET L17 HAS BEEN SAVED AS 'CHIMERIC/A'

=> d l17 1-66 bib ab

L17  ANSWER 1 OF 66  CA  COPYRIGHT 2003 ACS
AN   138:54547  CA
TI   TRX1 antibodies for inducing immune tolerance and treating organ graft
     rejection
IN   Frewin, Mark; Waldmann, Herman; Gorman, Scott; Hale, Geoff; Rao, Patricia;
     Kornaga, Tadeusz; Ringler, Douglas; Cobbold, Stephen; Winsor-Hines, Dawn
PA   Isis Innovation Limited, UK; Cambridge University Technical Services
     Limited; Tolerrx Inc.
SO   PCT Int. Appl., 131 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
PI   WO 2002102853      A2   20021227      WO 2002-GB2796   20020614
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
             TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     GB 2376466         A1   20021218      GB 2001-14517    20010614
     GB 2376467         A1   20021218      GB 2001-22724    20010920
PRAI GB 2001-14517      A    20010614
     GB 2001-22724      A    20010920
     US 2001-345194P    P    20011019
     US 2002-373470P    P    20020418
     US 2002-373471P    P    20020418
AB   Provided is a method for inducing immune tolerance in a primate by use of
     a compd. that reduces the amt. of CD4+CD25+ cells in a primary mixed
     lymphocyte reaction and IL-2, IL-4 and IL-12 in a secondary mixed
     lymphocyte reaction.  The compds. are preferably TRX1 antibodies (
     humanized antibodies of mouse monoclonal anti-
     CD4 antibody NSM 4.7.2.4), and the compds. are preferably used in
     accordance with a specified dosing regimen.  The invention also include a
     process for screening a compd for use in inducing immune tolerance.

L17  ANSWER 2 OF 66  CA  COPYRIGHT 2003 ACS
AN   138:3446  CA
TI   Expression of anti-CD4 human/murine chimeric
     antibody and its anti-proliferative effects against PBMC
AU   Zhu, Zhigang; Shen, Guanxin; Zhu, Huifen; Zhang, Yue; Shao, Jingfang;
```

Yang, Jing
CS Institute of Immunology, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, Peop. Rep. China
SO Zhonghua Weishengwuxue He Mianyixue Zazhi (2002), 22(2), 134-138
CODEN: ZWMZDP; ISSN: 0254-5101
PB Weishenbu Beijing Shengwu Zhipin Yanjiuso
DT Journal
LA Chinese
AB The anti-**CD4** murine **chimeric antibody** was prepd. and its anti-proliferative effects were studied. Total RNA was extd. from the murine hybridoma cell line secreting anti-CD4 monoclonal antibody (McAb). VH and VL genes were amplified by RT-PCR. The PCR products were cloned into pGEM-T vectors, then transfected into JM109. VH and VL genes were analyzed by automatic DNA sequencer. VH and VL genes were subcloned into p.gamma.1-Expr and pk- Epxr, resp., then transfected into XL2-Blue. The VH-p.gamma.1 and VL-pk were cotransfected into mouse myeloma cell X63Ag8.653 by electroporation. The transfectoma cells were selected by G418 screening and then supernatant of cultured transfectoma was analyzed by ELISA and immunofluorescence techniques. The transfectoma cells secreting anti-**CD4 chimeric antibodies** were collected. These chimeric antibodies can inhibit the proliferation of PBMC induced by phytohemagglutinin (PHA) and IL-2 in vitro. Human/murine chimeric antibodies were potential candidates for inhibition of transplant rejection and immunotherapy of autoimmune diseases.

L17 ANSWER 3 OF 66 CA COPYRIGHT 2003 ACS
AN 137:31732 CA
TI Asthma refractory to glucocorticoids: The role of newer immunosuppressants
AU Corrigan, Chris J.
CS Department of Respiratory Medicine & Allergy, Guy's, King's and St. Thomas' School of Medicine, Guy's Hospital, London, UK
SO American Journal of Respiratory Medicine (2002), 1(1), 47-54
CODEN: AJRMAG; ISSN: 1175-6365
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review. Asthma is orchestrated by cytokine products of activated T cells. Glucocorticoids are thought to ameliorate asthma at least partly through T cell inhibition. Consequently, other T cell immunomodulatory agents have been assessed for asthma therapy. Since these agents may have serious unwanted effects, attention has been focused on patients with severe asthma refractory to maximal topical, and addnl. systemic glucocorticoid therapy. Although gold salts show a modest but significant glucocorticoid-sparing effect in severe asthma, lung function is not improved and not all patients respond. The min. duration of a valid trial of therapy is probably 6 mo. Unwanted effects include dermatitis, hepatic dysfunction, proteinuria and interstitial pneumonitis. Meta-anal. of trials of methotrexate in oral glucocorticoid-dependent asthma have confirmed that concomitant weekly methotrexate for a min. of 3 to 6 mo enables significant (approx. 20%) overall redn. in oral glucocorticoid requirements, although only approx. 60% of patients show a significant response. There is little effect on lung function. Blood count and liver function must be monitored. Opportunistic infection is rare but potentially fatal. Cyclosporine, administered for at least 3 mo, is effective in only a proportion of patients with oral glucocorticoid-dependent asthma, where it may improve disease severity and/or enable oral glucocorticoid dosage redns. Regular monitoring of renal function, blood pressure and blood concns. of cyclosporine is required. The evidence that i.v. Ig (Ig) is of any benefit in patients with glucocorticoid-dependent asthma is at present equivocal. The therapy is expensive and assocd. with a high incidence of unwanted effects (fever, aseptic meningitis, urticaria). The macrolides tacrolimus (FK506) and sirolimus (rapamycin) have end effects similar to those of cyclosporine. Brequinar sodium, mycophenolate mofetil and leflunomide are inhibitors of de novo synthesis

of pyrimidines and purines, to which T cells are particularly sensitive. Such drugs may in theory be beneficial for therapy of patients with oral glucocorticoid-dependent asthma. **Humanized anti-CD4**, anti-IgE and anti-interleukin (IL)-5 monoclonal antibodies, and other cytokine inhibitors such as sol. IL-4 receptor have entered early trials. The worth of current immunomodulatory drugs is limited since: (i) not all patients respond, and response cannot be predicted a priori; (ii) the high incidence of unwanted effects makes it difficult to assess overall benefit/risk ratios; (iii) there is increased risk of opportunistic infection and (theor.) neoplasia; (iv) there. Are many relative and abs. contraindications to therapy; and (v) there is lack of knowledge about the long-term effects, beneficial or otherwise, of therapy.

RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 66 CA COPYRIGHT 2003 ACS
AN 136:165691 CA
TI Mechanism of anti-CD4 antibodies inhibitory effect on SEB- induced PBMC proliferation
AU Zhang, Zhihong; Shen, Guanxin; Yang, Jing; Zhu, Huifen; Zhang, Yue
CS Department of Immunology, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, 430030, Peop. Rep. China
SO Zhongguo Mianyixue Zazhi (2001), 17(4), 176-179
CODEN: ZMZAEE; ISSN: 1000-484X
PB Zhongguo Mianyixue Zazhi Bianjibu
DT Journal
LA Chinese
AB The inhibitory effect of anti-CD4 antibodies on Staphylococcal enterotoxin B (SEB)-induced proliferation of peripheral blood mononuclear cells (PBMC) was studied. The effect of anti-CD4 antibodies effect on PBMC proliferation in different conditions was obsd. by MTT method. CD4+ T cells apoptosis induced by anti-CD4 antibodies were detd. by morphol., biochem. and flow cytometric methods. The SEB-induced PBMC proliferation was inhibited by both anti-CD human/murine **chimeric antibodies** and murine McAbs, and **CD4**+ T cells apoptosis was induced specially by anti-**CD4 chimeric antibodies**. The results showed that anti-CD4 antibody may directly inhibit TCR-induced early activation signals, the inhibitory effect of anti-**CD4 chimeric antibodies** was closely related to monocytes, and further crosslinking of anti-CD4 antibodies was important for inducing CD4+ T cell apoptosis.

L17 ANSWER 5 OF 66 CA COPYRIGHT 2003 ACS
AN 135:341184 CA
TI Antibodies specific for CD4-binding domain of HIV-1
IN Chang, Tse Wen; Fung, Michael S. C.; Sun, Bill N. C.; Sun, Cecily R. Y.; Chang, Nancy T.
PA Tanox, Inc., USA
SO U.S., 11 pp., Cont.-in-part of U.S. Ser. No. 531,789, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6309880	B1	20011030	US 1993-89990	19930709
PRAI	US 1989-342950	B2	19890425		
	US 1990-531789	B2	19900612		

AB A particular epitope located within the CD4-binding region of gp120 of HIV-1, and antibodies specific for the epitope which can inhibit HIV-1 infection of human cells by diverse strains and isolates of the virus, is disclosed. The antibodies are useful for a no. of purposes, including diagnosis of HIV-1 infection.

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 6 OF 66 CA COPYRIGHT 2003 ACS
AN 135:191023 CA
TI Cloning and sequencing of VH/VL genes of anti-CD4 McAb
AU Zhu, Zhigang; Shen, Guanxin; Zhu, Huifen; Wang, Xiaolin; Zhang, Yue; Gong, Feili; Mao, Ping
CS Department of Hematology, Guangzhou First Municipal People's Hospital, Canton, 510180, Peop. Rep. China
SO Guangdong Yixue (2000), 21(8), 636-638
CODEN: GUYIEG; ISSN: 1001-9448
PB Guangdongsheng Yixue Qingbao Yanjiuso
DT Journal
LA Chinese
AB Variable region gene of anti-CD4 monoclonal antibody for construction of anti-**CD4 chimeric antibody** was obtained.
Total RNA was prepd. from the mouse hybridoma cell line that secrets antibody against CD4. The VH and VL genes were amplified by RT-PCR with family specific primer pairs. The PCR products were cloned into pGEM-T vectors, then transfected into JM109. The VH and VL genes were analyzed by automatic DNA sequencer. The results showed that VH of the anti-CD4 McAb consists of 351 bp encoding 117 amino acid residues, and VL of the anti-CD4 McAb contains 333 bp encoding 11 amino acid residues. According to Kabat classification, the VH and VL genes belong to the mouse Ig heavy chain subgroup II (A) and k chain subgroup III, resp. The deduced amino acid sequences of the VH/VL are in agreement with the characterization of the amino acid present in the mouse Ig variable region.

L17 ANSWER 7 OF 66 CA COPYRIGHT 2003 ACS
AN 135:59899 CA
TI CD4+ T cell apoptosis induced by anti-CD4 antibodies
AU Zhang, Zhihong; Zhang, Yue; Zhu, Huifen; Yang, Jing; Shen, Guanxin
CS Department of Immunology, Tongji Medical University, Wuhan, 430030, Peop. Rep. China
SO Journal of Tongji Medical University (2000), 20(2), 100-102
CODEN: JTMUEI; ISSN: 0257-716X
PB Tongji Medical University
DT Journal
LA English
AB To explore the inhibitory effects of anti-**CD4** human/murine **chimeric antibodies** on lymphocyte proliferation, **CD4**+ T cell apoptosis induced by anti-CD4 antibodies was examd. Annexin-V-FITC and PI double stain method was employed to qual. and quant. detd. CD4+ T cell apoptosis induced by anti-CD4 antibodies. Our results showed that anti-**CD4 chimeric antibodies** could specifically induce **CD4**+ T cell apoptosis. The ability of anti-**CD4 chimeric antibodies** to induce **CD4**+ T cell apoptosis was related with the presence of monocytes. It is concluded that the further crosslinking of anti-CD4 antibodies is important for inducing CD4+ T cell apoptosis.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 8 OF 66 CA COPYRIGHT 2003 ACS
AN 134:320414 CA
TI Gene therapy and HIV-1 infection: experimental approaches, shortcomings, and possible solutions
AU Dornburg, Ralph; Pomerantz, Roger
CS The Dorrance H. Hamilton Laboratories, Center for Human Virology, Division of Infectious Diseases, Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, 19107, USA
SO Human Retroviral Infections (2000), 307-323. Editor(s): Ugen, Kenneth E.; Bendinelli, Mauro; Friedman, Herman. Publisher: Kluwer Academic/Plenum

Publishers, New York, N. Y.
CODEN: 69AQHO
DT Conference; General Review
LA English
AB A review with 110 refs. Topics discussed include studies on HIV-1 infection and conventional pharmaceutical agents; antisense RNAs and ribozymes; RNA decoys; transdominant mutant proteins; toxic genes; **CD4** as decoy; **single-chain antibodies** ; and gene delivery of antiviral agents.
RE.CNT 110 THERE ARE 110 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 66 CA COPYRIGHT 2003 ACS
AN 134:279285 CA
TI Local production of anti-CD4 antibody by transgenic allogeneic grafts affords partial protection
AU Zhan, Yifan; Martin, Roland M.; Sutherland, Robyn M.; Brady, Jamie L.; Lew, Andrew M.
CS Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia
SO Transplantation (2000), 70(6), 947-954
CODEN: TRPLAU; ISSN: 0041-1337
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Background. Immunosuppressive drugs and anti-lymphocyte antibody are used clin. to suppress cellular rejection responses. However, these systemic regimens often led to general immunodeficiency and thus increased susceptibility to opportunistic infection and neoplasia. Immunosuppressive mols. delivered locally may be a way of inhibiting rejection responses, whereas systemic immunity is preserved. To achieve protective local immunosuppression, we produced a graft secreting its own immunomodulator, by deriving transgenic mice expressing a **chimeric anti-CD4** antibody (GK2c) in the pancreas. Methods and Results. Transgenic mice in bm1 genetic background expressing a modified anti-mouse CD4 antibody (GK2c) under two promoters have been produced. Tissue expression of GK2c was detected by immunoperoxidase staining. Under the cytomegalovirus promoter, there was abundant GK2c expression in pancreatic exocrine tissue. Under the rat preproinsulin II promoter, there was abundant GK2c expression in pancreatic endocrine tissue only. High-expression transgenic lines had 10-100 .mu.g/mL GK2c in blood plasma. By flow cytometry, these transgenic mice were devoid of CD4+ cells in their peripheral lymphoid organs. To test transgenic mice as donors, fetal pancreata from transgenic mice were grafted into fully allogeneic CBA mice under the kidney capsule, transgenic grafts had prolonged survival compared with control non-transgenic grafts. Furthermore, GK2c transgenic grafts had reduced infiltration with an absence of CD4+ cells at the graft site without any effect on the cell compn. in lymphatic tissues. Conclusion. Transgenic grafts that secrete anti-CD4 antibody can afford some protection against graft rejection, while only affecting the CD4 population at the graft site.
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 10 OF 66 CA COPYRIGHT 2003 ACS
AN 134:161812 CA
TI Prolonged allograft survival in anti-CD4 antibody transgenic mice: lack of residual helper T cells compared with other CD4-deficient mice
AU Han, Wen-Ruo; Zhan, Yifan; Murray-Segal, Lisa J.; Brady, Jamie L.; Lew, Andrew M.; Mottram, Patricia L.
CS Department of Surgery, Royal Melbourne Hospital, University of Melbourne, Parkville, 3050, Australia
SO Transplantation (2000), 70(1), 168-174
CODEN: TRPLAU; ISSN: 0041-1337
PB Lippincott Williams & Wilkins

DT Journal
LA English
AB Background. Investigations of the role of CD4 T lymphocytes in allograft rejection and tolerance have relied on the use of mouse models with a deficiency in CD4 cells. However, in mice treated with depleting monoclonal antibody (mAb) and in MHC class II knockout (KO) mice, there are residual populations of CD4 cells. CD4 KO mice had increased CD4- CD8- TCR.alpha..beta.+ helper T cells, and both strains of KO mice could reject skin allografts at the normal rate. In this study, transgenic mice with no peripheral CD4 cells were the recipients of skin and heart allografts. Results were compared with allograft survival in CD4 and MHC class II KO mice. Methods. GK5 (G57BL/6 bm1 mice transgenic for a **chimeric anti-CD4** antibody) had no peripheral CD4 cells. These mice, and CD4 and class II KO mice, received BALB/c or CBA skin or cardiac allografts. Some GK5 mice were treated with anti-CD8 mAb to investigate the role of CD8 cells in rejection. CD4 and CD8 cells were assessed by FACS and immunohistochem. Results. BALB/c skin on GK5 mice had a mean survival time .+-. SD of 24.+-.6 days, compared with 9.+-.2 days in wild-type mice. Anti-CD8 mAb prolonged this to 66.+-.7 days. BALB/c skin survived 10.+-.2 days on class II KO and 14.+-.2 days on CD4 KO, both significantly less than the survival seen on GK5 recipients ($P<0.001$). BALB/c hearts survived >100 days in GK5 recipients and in wild-type recipients treated with anti-CD4 mAb at the time of grafting, in contrast to a mean survival time of 10.+-.2 days in untreated wild-type mice. Immunohistochem. revealed that long-term surviving heart allografts from the GK5 recipients had CD8 but no CD4 cellular infiltrate. These hearts showed evidence of transplant vasculopathy. Conclusions. The GK5 mice, with a complete absence of peripheral CD4 cells, provide the cleanest available model for investigating the role of CD4 lymphocytes in allograft rejection. Prolonged skin allograft survival in these mice compared with CD4 and MHC class II KO recipients was clearly the result of improved CD4 depletion. Nevertheless, skin allograft rejection, heart allograft infiltration, and vascular disease, mediated by CD8 cells, developed in the absence of peripheral CD4 T cells.
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 11 OF 66 CA COPYRIGHT 2003 ACS
AN 134:3853 CA
TI Local secretion of a **chimeric anti-CD4** antibody protects against graft rejection in the NOD mouse
AU McKenzie, Andrew W.; Brady, Jamie L.; Martin, Roland M.; Georgiou, Harry M.; Lew, Andrew M.
CS Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Parkville, 3050, Australia
SO Transplantation (2000), 69(8), 1745-1748
CODEN: TRPLAU; ISSN: 0041-1337
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Background. Engineering a graft to secrete its own immunosuppressive antibodies may minimize the risks assocd. with current high dose systemic immunosuppression. Methods and Results. A .beta. cell insulinoma cell line (NIT-1) was transfected with genes encoding a **chimeric anti-CD4** antibody. The NIT-1 cells secreted functional **chimeric anti-CD4** antibody that bound to the CD4 mol. on mouse thymocytes and inhibited in vitro proliferation of CD4+ve T cells. Both test and control transfected cell lines grew at a similar rate in immunodeficient mice. In immunocompetent NOD mice, NIT-1 cells are normally rejected by a cellular immune response against the SV40 T antigen. Although control transfected NIT-1 cells were rapidly rejected by NOD mice, anti-CD4 secreting NIT-1 cells grew significantly better and were able to form tumors at the site of injection. Conclusions. The local secretion of **chimeric anti-CD4** antibody from

transfected cells can contribute to graft survival in our transplantation model.

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 12 OF 66 CA COPYRIGHT 2003 ACS
AN 133:334049 CA
TI Recombinant anti-CD4 antibodies for human therapy
IN Hanna, Nabil; Newman, Roland Anthony; Reff, Mitchell Elliot
PA IDEC Pharmaceuticals Corporation, USA
SO U.S., 82 pp., Cont.-in-part of U.S. 5,756,096.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6136310	A	20001024	US 1995-523894	19950906
	EP 1266965	A2	20021218	EP 2002-12106	19920724
	EP 1266965	A3	20030102		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC				
	ZA 9205615	A	19930428	ZA 1992-5615	19920727
	TW 393489	B	20000611	TW 1992-81105967	19920728
	US 5658570	A	19970819	US 1995-379072	19950125
	US 5756096	A	19980526	US 1995-476237	19950607
	CA 2231182	AA	19970313	CA 1996-2231182	19960905
	WO 9709351	A1	19970313	WO 1996-US14324	19960905
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
	AU 9669162	A1	19970327	AU 1996-69162	19960905
	AU 717674	B2	20000330		
	EP 854885	A1	19980729	EP 1996-929936	19960905
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1200737	A	19981202	CN 1996-197943	19960905
	BR 9610404	A	19990706	BR 1996-10404	19960905
	JP 11514216	T2	19991207	JP 1996-511411	19960905
	NO 9800915	A	19980506	NO 1998-915	19980303
PRAI	US 1991-735064	B2	19910725		
	US 1992-856281	B2	19920323		
	US 1992-912292	B1	19920710		
	US 1995-379072	A2	19950125		
	US 1995-476237	A2	19950607		
	EP 1992-917108	A3	19920724		
	US 1995-523894	A	19950906		
	WO 1996-US14324	W	19960905		

AB **Chimeric antibodies** specific to human **CD4** antigen, DNA encoding, pharmaceutical compns. contg. and use thereof as therapeutic agents are taught. These chimeric antibodies contain Old World monkey variable sequences and human const. domain sequences, preferably human gamma 1, gamma 4 or mutated forms thereof. These antibodies possess desirable therapeutic properties including low antigenicity, reduced (or absent) T cell depleting activity, good affinity to human CD4 and enhanced stability (in vivo half-life).

RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 13 OF 66 CA COPYRIGHT 2003 ACS
AN 133:206541 CA

TI Identification of anti-**CD4 chimeric antibody** and detection of its effects on PBMC proliferation
AU Zhang, Zhihong; Shen, Guanxin; Yang, Jing; Zhu, Huifen; Zhang, Yue
CS Department of Immunology, Tongji Medical University, Wuhan, 430030, Peop. Rep. China
SO Mianyixue Zazhi (2000), 16(4), 265-267
CODEN: MIZAED; ISSN: 1000-8861
PB Mianyixue Zazhi Bianjibu
DT Journal
LA Chinese
AB The biol. characteristics of the anti-**CD4** human/murine **chimeric antibody** was identified, and their inhibitory effects on the peripheral blood mononuclear cells (PBMC) proliferation induced by anti-CD3 McAb or EBV transformed cell were studied by using indirect immunofluorescence competed inhibiting expt. and MTT test for detection of their inhibitory effects. Transfected hybridoma had the ability to stably express and secrete specific anti-**CD4** human/murine **chimeric antibody**. Chimeric antibody had the same relative affinity as murine McAb. PBMC proliferation induced by TCR approach was inhibited by both the anti-**CD4 chimeric antibody** and murine McAb, preferably chimeric antibody. The results showed that the anti-CD4 antibody may inhibit PBMC proliferation via direct effect on TCR-induced activation signals.

L17 ANSWER 14 OF 66 CA COPYRIGHT 2003 ACS
AN 133:57280 CA
TI Blockade of T cell activation using a surface-linked single-chain antibody to CTLA-4 (CD152)
AU Griffin, Matthew D.; Hong, David K.; Holman, Philmore O.; Lee, Kyung-Mi; Whitters, Matthew J.; O'Herrin, Sean M.; Fallarino, Francesca; Collins, Mary; Segal, David M.; Gajewski, Thomas F.; Kranz, David M.; Bluestone, Jeffrey A.
CS The Ben May Institute for Cancer Research, University of Chicago, Chicago, IL, 60637, USA
SO Journal of Immunology (2000), 164(9), 4433-4442
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB CTLA-4 (CD152) engagement can down-regulate T cell activation and promote the induction of immune tolerance. However, the strategy of attenuating T cell activation by engaging CTLA-4 has been limited by sharing of its natural ligands with the costimulatory protein CD28. In the present study, a CTLA-4-specific single-chain Ab (scFv) was developed and expressed on the cell surface to promote selective engagement of this regulatory mol. Transfectants expressing anti-CTLA-4 scFv at their surface bound sol. CTLA-4 but not sol. CD28. Coexpression of anti-CTLA-4 scFv with anti-CD3.epsilon. and anti-CD28 scFvs on artificial APCs reduced the proliferation and IL-2 prodn. by resting and preactivated bulk T cells as well as CD4+ and CD8+ T cell subsets. Importantly, expression of anti-CTLA-4 scFv on the same cell surface as the TCR ligand was essential for the inhibitory effects of CTLA-4-specific ligation. CTLA-4-mediated inhibition of tyrosine phosphorylation of components of the proximal TCR signaling app. was similarly dependent on coexpression of TCR and CTLA-4 ligands on the same surface. These findings support a predominant role for CTLA-4 function in the modification of the proximal TCR signal. Using T cells from DO11.10 and 2C TCR transgenic mice, neg. regulatory effects of selective CTLA-4 ligation were also demonstrated during the stimulation of Ag-specific CD4+ and CD8+ T cells by MHC/peptide complexes. Together these studies demonstrate that selective ligation of CTLA-4 using a membrane-bound scFv results in attenuated T cell responses only when coengaged with the TCR during T cell/APC interaction and define an approach to harnessing the immunomodulatory potential of CTLA-4-specific ligation.

RE.CNT 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 15 OF 66 CA COPYRIGHT 2003 ACS
AN 133:3714 CA
TI Humanized antibody specific for human 4-1bb and pharmaceutical composition comprising same
IN Hong, Hyo Jeong; Park, Sung Sup; Kang, Young Jun; Kang, Chang Yuil; Yoon, Sung Kwan
PA LG Chemical Limited, S. Korea
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000029445	A1	20000525	WO 1999-KR689	19991117
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	KR 2000034847	A	20000626	KR 1999-16750	19990511
	EP 1131357	A1	20010912	EP 1999-972226	19991117
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002531383	T2	20020924	JP 2000-582430	19991117
PRAI	KR 1998-49177	A	19981117		
	KR 1999-16750	A	19990511		
	WO 1999-KR689	W	19991117		

AB The present invention is directed to humanized antibodies that specifically bind the protein 4-1BB. The antibodies can be made by grafting of the complementarity detg. regions (CDR's) of mouse monoclonal antibody to human 4-1BB to the remaining portions of a human antibody and by making further amino acid replacements. In addn., a pharmaceutical compn. that includes the humanized antibody can be made and can be used to treat autoimmune diseases to suppress an immune response. The humanized antibody of the invention has high affinity for human 4-1BB, and exhibits sequence similarity to human antibody. As a result, the pharmaceutical compn. of the present invention can be used to treat autoimmune disease and act as an immunosuppressant in humans without much side-effect.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 16 OF 66 CA COPYRIGHT 2003 ACS
AN 132:193037 CA
TI New antibody therapy for rheumatoid arthritis. I
AU Hakoda, Masayuki
CS Inst. Rheumatol., Tokyo Women's Med. Coll., Japan
SO Ensho to Men'eki (1999), 7(5), 558-563
CODEN: ENMEFA; ISSN: 0918-8371
PB Sentan Igakusha
DT Journal; General Review
LA Japanese
AB A review with 20 refs. on clin. trials of antibody therapy for rheumatoid arthritis with mouse anti-CD4 monoclonal antibody and **chimeric anti-CD4** monoclonal antibody.

L17 ANSWER 17 OF 66 CA COPYRIGHT 2003 ACS

AN 132:34763 CA
TI Monoclonal antibody to human CD4 antigen and preparation of single-chain antiodies
IN Ono, Mitsuharu; Kusaka, Takayuki; Morimoto, Ikuo
PA Asahi Chemical Industry Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 25 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 11332563	A2	19991207	JP 1998-163034	19980526
PRAI JP 1998-163034		19980526		

AB Mouse monoclonal antibody 4H5 having high affinity and specificity toward human CD4 are reported. Amino acid sequences of the complementarity detg. regions (CDR), CDR-1, CDR-2, and CDR-3 of Heavy and Light chain variable regions of the antibody are disclosed. Prepn. of secretion-type single-chain antibodies (ScFv) comprising VL-VH or VH-VL in transgenic COS7 cells was shown. The cDNA encoding the variable regions of 4H5 may be used for the prepn. of humanized antibodies by substituting the Fc region with the human counterpart.

L17 ANSWER 18 OF 66 CA COPYRIGHT 2003 ACS
AN 131:350076 CA
TI Anti-proliferative effects induced by anti-**CD4** human/murine **chimeric antibody** and murine anti-**CD4** monoclonal antibody
AU Shen, Guanxin; Zhu, Huifen; Wang, Xiaolin; Zhang, Yue; Zhu, Zhigang; Wang, Shuo
CS Department of Immunology, Tongji Medical University, Wuhan, 430030, Peop. Rep. China
SO Journal of Tongji Medical University (1999), 19(1), 6-9
CODEN: JTMUEI; ISSN: 0257-716X
PB Tongji Medical University
DT Journal
LA English
AB The effects of **chimeric anti-CD4** human/murine **chimeric antibody** and murine anti-**CD4** monoclonal antibody (McAb) on the proliferation induced by anti-CD3 McAb, phytohemagglutinin (PHA), IL-2, and allogeneic cells were studied. The results showed that **chimeric anti-CD4** antibody and murine anti-CD4 McAb could inhibit the proliferation induced by the above inducers and the inhibitory effects were related to the dosage of the antibodies.
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 19 OF 66 CA COPYRIGHT 2003 ACS
AN 131:241552 CA
TI New therapeutic targets for rheumatoid arthritis
AU Dinant, H. J.; Dijkmans, B. A. C.
CS Department of Rheumatology, Jan van Breemen Institute, Amsterdam, 1056 AB, Neth.
SO Pharmacy World & Science (1999), 21(2), 49-59
CODEN: PWSCED; ISSN: 0928-1231
PB Kluwer Academic Publishers
DT Journal; General Review
LA English
AB A review with 109 refs. New insights into the pathogenesis of rheumatoid arthritis (RA) and consequently new targets of therapy are covered in a broad overview fashion. Short-term significant beneficial effect on RA disease activity has been established in a small but rapidly growing no. of double-blind placebo-controlled trials now including recombinant human

IL-1 receptor antagonist, chimeric (mouse/human) monoclonal antibodies (mAb) against TNF.alpha. (cA2), humanized (human/mouse) anti-TNF.alpha. mAb (CDP571) and recombinant human TNF-receptor-Fc fusion protein (TNFR:Fc). Placebo-controlled trials of anti-T cells agents such as **chimeric anti-CD4** mAb (cM-T412) and anti-CD5 immunoconjugate, did not demonstrate clin. benefit. A placebo-controlled study of the anti-T cell derived cytokine IL-2 (DAB486IL-2) showed only modest clin. improvement. Other anti-T cell approaches such as autologous T cell vaccination and induction of tolerance by oral type II collagen have been unsuccessful. The one controlled trial with an anti-inflammatory cytokine, recombinant human IFN-.gamma., showed modest clin. benefits. Controlled trials with IL-4 and IL-10 and with anti-adhesion mols. are awaited.

RE.CNT 109 THERE ARE 109 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 20 OF 66 CA COPYRIGHT 2003 ACS
AN 130:152295 CA
TI Reduction of Th1 cell activity in the peripheral circulation of patients with rheumatoid arthritis after treatment with a non-depleting humanized monoclonal antibody to CD4
AU Schulze-Koops, Hendrik; Davis, Laurie S.; Haverty, Thomas P.; Wacholtz, Mary C.; Lipsky, Peter E.
CS Rheumatic Diseases Division, Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Raritan, NJ, USA
SO Journal of Rheumatology (1998), 25(11), 2065-2076
CODEN: JRHUA9; ISSN: 0315-162X
PB Journal of Rheumatology Publishing Co. Ltd.
DT Journal
LA English
AB Objective: To test the hypothesis that administration of a non-depleting monoclonal antibody (Mab) to CD4 may alter T cell function in patients with rheumatoid arthritis (RA), possibly assocd. with clin. benefit. The patients with RA treated were a subset from a multicenter, placebo-controlled, randomized, double-blind trial and were randomized into one of 2 treatment groups receiving placebo or .+-. 450 mg of a **humanized anti-CD4** Mab (ORTHOCLONE OKTcdr4a) per wk for 2 treatment cycles. For the third cycle, patients who had received Mab during the first 2 courses were given placebo, whereas the patients who were originally given placebo received anti-CD4 Mab. To evaluate the impact of anti-CD4 Mab treatment on T cell functions, cytokine prodn. by mitogen-stimulated peripheral blood T cells was monitored, cytokine mRNA levels were assessed in stimulated peripheral blood mononuclear cells (PBMC) by semiquant. polymerase chain reaction, and clin. activity was also measured during the study. Administration of the anti-CD4 Mab, but not placebo, was followed by an immediate transient clin. benefit accompanied by a significant decrease in C-reactive protein levels. There was no significant change in the no. of circulating CD4+ T cells. However, 7 wk after the second Mab treatment, interleukin 2 (IL-2) and IFN-.gamma. mRNA levels were significantly reduced in all anti-CD4 Mab treated patients, but neither was reduced in placebo-treated patients. Clin. improvement in patients with RA treated with a non-depleting Mab to CD4 may be related to a decrease in the function of IL-2 and IFN-.gamma. producing Th1 cells.

RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 21 OF 66 CA COPYRIGHT 2003 ACS
AN 130:94193 CA
TI Randomized, dose-ranging, placebo-controlled study of **chimeric antibody** to **CD4** (keliximab) in chronic severe asthma
AU Kon, Onn M.; Sihra, Bhupinder S.; Compton, Christopher H.; Leonard, Thomas B.; Kay, A. Barry; Barnes, Neil C.
CS London Chest Hospital, London, E2 9JX, UK

SO Lancet (1998), 352(9134), 1109-1113
CODEN: LANCAO; ISSN: 0140-6736
PB Lancet Ltd.
DT Journal
LA English
AB There is substantial circumstantial evidence that CD4 lymphocytes have a role in the pathogenesis of chronic asthma. We investigated the efficacy and safety in severe corticosteroid-dependent asthma of a single i.v. infusion of keliximab (IDEC CE9.1), a chimeric monoclonal antibody to CD4. 22 Patients were recruited from two asthma clinics. In an ascending-dose design, the first eight patients were assigned 0.5 mg/kg keliximab (six) or placebo (two); the next seven were assigned 1.cntdot.5 mg/kg (five) or placebo (two); and the last seven were assigned 3.cntdot.0 mg/kg (five) or placebo (two). Masked data on safety for each dose group were assessed before progression to the next dose. Patients kept a daily symptom diary and measured morning and evening peak expiratory flow (PEF) at home. PEF and forced expiratory vol. in 1 s (FEV1) were measured at follow-up clinic visits. Patients given 0.cntdot.5 mg/kg or 1.cntdot.5 mg/kg keliximab and placebo recipients did not differ in change from baseline of PEF, FEV1, or symptom score. Those given 3.cntdot.0 mg/kg keliximab differed significantly from placebo recipients in change in morning PEF (median area under curve [AUC] 445 vs -82.cntdot.5, p=0.005) and evening PEF (median AUC 548 vs -85, p=0.014). Sympton score showed the same pattern (though differences did not achieve significance), but there was no difference in clinic FEV1. There were no serious adverse effects related to treatment. Two patients had mild exacerbations of eczema and one developed a transient maculopapular rash. All doses of keliximab were assocd. with a redn. from baseline in CD4 count. Our findings raise the possibility that T-cell-directed treatment may be an alternative approach to the treatment of severe asthma.
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 22 OF 66 CA COPYRIGHT 2003 ACS
AN 130:37047 CA
TI Expression of anti-**CD4** human/murine **chimeric antibody** and its killer tumor activity
AU Shen, Guanxin; Zhu, Zhigang; Zhu, Huifen; Shao, Jingfang; Wang, Xiaolin; Xiong, Wei
CS Dep. of Immunology, Tongji Medical University, Wuhan, 430030, Peop. Rep. China
SO Journal of Tongji Medical University (1998), 18(1), 1-4
CODEN: JTMUEI; ISSN: 0257-716X
PB Tongji Medical University
DT Journal
LA English
AB From the mouse hybridoma cell line secreting an anti-CD4 monoclonal antibody (McAB), total RNA was prepd. The VH and VL genes were amplified by RT-PCR with family specific primer pairs. The PCR products were cloned into pGEM-T vectors, then transfected into JM109. The VH an VL genes were analyzed by automatic DNA sequencer. According to Kabat classification, the VH and VL genes belong to the mouse Ig heavy subgroup II (A) and .kappa. chain subgroup III, resp. The VH and VL genes were subcloned into p.gamma.1-Expr and p.kappa.-Expr resp., then transfected into XL2-Blue. The VH-p.gamma.1 and VL-p.kappa. were transfected by electroporation into mouse myeloma cell X63Ag8. 653. The transfectoma cells were selected by G418 screening, and then supernatant of cultured transfectoma was analyzed by ELISA and immunofluorescence techniques. We have acquired transfectoma cells secreting anti-**CD4 chimeric antibodies**. These chimeric antibodies are able to kill tumor cells specifically in vitro.
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 23 OF 66 CA COPYRIGHT 2003 ACS
AN 129:301429 CA
TI Prolongation of cardiac graft survival with anti-CD4Ig plus hCTLA4Ig in primates
AU Krieger, Nancy R.; Yuh, David; McIntyre, W. Burley; Flavin, Thomas F.; Yin, Dengping; Robbins, Robert; Fathman, C. Garrison
CS Department of Surgery and Department of Medicine, Division of Immunology, Stanford University Medical Center, Stanford, CA, 94305, USA
SO Journal of Surgical Research (1998), 76(2), 174-178
CODEN: JSGRA2; ISSN: 0022-4804
PB Academic Press
DT Journal
LA English
AB The aim of this study was to det. whether the use of combined immunotherapy with a brief course of humanized anti-CD4Ig and hCTLA4Ig would prolong heterotopic cardiac allograft survival in primates (rhesus monkeys). This model was based on work in "high responder" rats where a brief course of depletive anti-CD4 mAb plus hCTLA4Ig was successful in inducing transplantation tolerance. Heterotopic cardiac transplants were performed in rhesus recipients. Donor/recipient pairs between groups were confirmed to be reactive prior to transplantation by MLR matching. Humanized anti-CD4Ig, a recently developed anti-CD4 mAb, was given at a dose of 20 mg/kg i.v. on days -3, -2, -1, and 0. HCTLA4Ig was administered at 6 mg/kg/dose i.v. on days 0 and 2 for the first recipient and days 0, 2, 4, and 6 for the second recipient. No further immunosuppression was administered. The treated or untreated recipients were followed for graft function by daily palpitation. Treatment with anti-CD4Ig plus hCTLA4Ig resulted in a significant prolongation of heart graft survival (42 days for the first recipient and 52 days for the second recipient) compared to untreated recipients (7 days .times. 4, 11 days .times. 1). FACS anal. demonstrated CD4 depletion of anti-CD4 treated animals to <2% on post-transplant day 1. The CD4+ T cells gradually repopulated to 50-70% pre-transplant levels just prior to rejection. No adverse responses (fever, tachypnea, tachycardia, infections) were obsd. These are the first results demonstrating that a brief course of combined specific induction immunotherapy with humanized anti-CD4Ig plus hCTLA4Ig, in the absence of adjuvant post-transplant immunosuppression, was well tolerated and resulted in marked prolongation of cardiac allograft survival in primates. (c) 1998 Academic Press.

L17 ANSWER 24 OF 66 CA COPYRIGHT 2003 ACS
AN 129:288912 CA
TI cDNA encoding a single-chain antibody to HIV p17 with cytoplasmic or nuclear retention signals inhibits HIV-1 replication
AU Tewari, Deepanker; Goldstein, Simoy L.; Notkins, Abner L.; Zhou, Paul
CS Oral Infection and Immunity Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, MD, 20892, USA
SO Journal of Immunology (1998), 161(5), 2642-2647
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB HIV-1 gag p17 protein is an attractive target for mol. intervention, because it is involved in the viral replication cycle at both the pre- and postintegration levels. In the present expts., the authors targeted p17 by intracellularly expressing a cDNA encoding an Ab to p17. CDNA from a hybridoma secreting Ab to p17 was cloned, sequenced, reconstructed as a single-chain Ab fragment (scFv), and expressed in the cytoplasm or nucleus with appropriate retention signals. The expressed scFvs had no effect on T cell growth or CD4 expression and bound specifically to HIV-1 p17. Human CD4+ Jurkat T cells that expressed scFvs and were infected with HIV-1 showed a marked redn. in virus replication compared with cells expressing vector alone. The inhibition of virus replication was more pronounced when scFvs were expressed in the cytoplasm rather than the

nucleus. From these studies, the authors conclude that the intracellular expression of a single-chain Ab to p17 inhibits HIV replication; in addn., the degree of inhibition is related to the intracellular targeting site.
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 25 OF 66 CA COPYRIGHT 2003 ACS
AN 129:274303 CA
TI The pharmacokinetics and human anti-mouse antibody response in rheumatoid arthritis patients treated with a **chimeric anti-CD4** monoclonal antibody
AU Choy, E. H. S.; Schantz, A.; Pitzalis, C.; Kingsley, G. H.; Panayi, G. S.
CS Rheumatology Unit, Division of Medicine, Guy's Hospital, UMDS, London, SE1 9RT, UK
SO British Journal of Rheumatology (1998), 37(7), 801-802
CODEN: BJRHDF; ISSN: 0263-7103
PB Oxford University Press
DT Journal; General Review
LA English
AB A review with 10 refs.

L17 ANSWER 26 OF 66 CA COPYRIGHT 2003 ACS
AN 129:3871 CA
TI Single-chain antibody chimeric receptors target cytotoxic effector cells against cancer
IN Greenburg, Gary B.; McArthur, James G.; Finer, Mitchell H.
PA Cell Genesys, Inc., USA; Greenburg, Gary B.; McArthur, James G.; Finer, Mitchell H.
SO PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9818809	A1	19980507	WO 1997-US18707	19971024
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9749058	A1	19980522	AU 1997-49058	19971024
	AU 744160	B2	20020214		
	EP 937095	A1	19990825	EP 1997-911757	19971024
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002512502	T2	20020423	JP 1998-520530	19971024
PRAI	US 1996-29029P	P	19961025		
	WO 1997-US18707	W	19971024		

AB The authors disclose the prepn. and biol. activity of chimeric proteins characterized by an antibody-based extracellular domain capable of binding to TAG-72, a transmembrane domain and a cytoplasmic domain capable of activating a signaling pathway in cytotoxic effector cells. Binding of TAG-72 to the extracellular domain results in transduction of a signal and activation of a signaling pathway in the cell, whereby the cell may be induced to carry out various functions relating to the signaling pathway. For example, T-cells were transduced with single-chain antibody fused to the transmembrane and cytoplasmic domains of CD3-.zeta.. Transduced cells exhibited cytolytic activity for a no. of gastrointestinal carcinoma cell lines expressing TAG-72.
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 27 OF 66 CA COPYRIGHT 2003 ACS
AN 128:320336 CA
TI Humanized IgG1 and IgG4 anti-CD4 monoclonal antibodies: Effects on lymphocytes in the blood, lymph nodes, and renal allografts in cynomolgus monkeys
AU Mourad, Georges J.; Preffer, Frederic I.; Wee, Siew-Lin; Powelson, John A.; Kawai, Tatsuo; Delmonico, Francis L.; Knowles, Robert W.; Cosimi, A. Benedict; Colvin, Robert B.
CS Immunopathology and Transplantation Units, Massachusetts General Hospital, Boston, MA, 02114, USA
SO Transplantation (1998), 65(5), 632-641
CODEN: TRPLAU; ISSN: 0041-1337
PB Williams & Wilkins
DT Journal
LA English
AB Optimizing therapeutic monoclonal antibody (mAb) depends on the incorporation of the necessary effector functions and the development of hypoantigenic "humanized" antibodies by genetic engineering, which then need to be tested in appropriate preclin. trials. Constructs of humanized OKT4A contg. the complementarity-detg. region (CDR) of murine OKT4A and the framework and const. regions of human light (.kappa.) and heavy chains (IgG1 and IgG4) were prepd. and tested in cynomolgus monkeys who received a renal allograft. A prophylactic course of CDR-OKT4A/human (h) IgG1 or CDR-OKT4A/hIgG4, either as high-dose single bolus (10 mg/kg) or as low-dose multiple infusion (1 mg/kg for 12 days) was given, and the effects on graft survival, immunohistol., circulating cells, and lymph node cells were assessed. The IgG1 isotype induced coating of T cells, modulation of surface CD4 mols., and profound depletion of CD4+ lymphocytes in peripheral blood, which persisted as long as the animals were followed (up to 7 wk). The IgG4 isotype induced only cell coating without cell clearance or modulation. In lymph nodes, coating of lymphocytes (approx. 60%) was seen with both isotypes in the earliest sample (6 h). After 2 days, significant depletion of lymph node CD4 cells was evident, with a decrease in the CD4 to CD8 ratio in the IgG1-treated group; no depletion occurred in the IgG4 group. The emigration of CD4+ cells into the allograft was significantly delayed in the CDR-OKT4A/hIgG1-treated animals when compared with the CDR-OKT4A/hIgG4 group as judged by immunocytochem. (23.8 days vs. 7.4 days) or interleukin-2-promoted T-cell outgrowth from allograft biopsies (22.2 days vs. 6.3 days). This study demonstrates that the in vivo effects of CDR-grafted OKT4A are dependent on its isotype. The depleting mAb CDR-OKT4A/hIgG1 significantly delays the entry of CD4+ cells into the graft, inhibiting the early phase of rejection. However, graft rejection occurs when CD4+ cells eventually infiltrate the graft, even in the presence of depressed levels of circulating CD4+ cells. Both isotypes demonstrated therapeutic efficacy: graft survival was prolonged over controls. In the case of CDR-OKT4A/hIgG4, neither lymphocyte depletion, antigenic modulation, nor prevention of infiltration is necessary for a beneficial effect, which indicates that this mAb blocks CD4 function or renders the CD4+ cell less responsive. The lack of depletion is a feature of potential clin. advantage in minimizing the risk of excessive immunosuppression.

L17 ANSWER 28 OF 66 CA COPYRIGHT 2003 ACS
AN 128:74314 CA
TI Antibodies against a complex of CD4 and a chemokine receptor domain, and their use against HIV infections
IN Wang, Chang Yi
PA United Biomedical, Inc., USA
SO PCT Int. Appl., 140 pp.
CODEN: PIXXD2
DT Patent

LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9746697	A2	19971211	WO 1997-US9449	19970603
	WO 9746697	A3	19971211		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5961976	A	19991005	US 1997-808374	19970228
	AU 9731529	A1	19980105	AU 1997-31529	19970603
	EP 910659	A2	19990428	EP 1997-926870	19970603
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	BR 9709524	A	20000509	BR 1997-9524	19970603
	JP 2000511775	T2	20000912	JP 1998-500752	19970603
PRAI	US 1996-657149	A	19960603		
	US 1997-808374	A	19970228		
	US 1997-867149	A	19970602		
	WO 1997-US9449	W	19970603		

AB This invention is directed to monoclonal antibodies produced by using CD4-expressing cells as immunogens. The monoclonal antibodies of the present invention are characterized by their ability to neutralize in vitro and in vivo primary isolates of human immunodeficiency virus (HIV) and related immunodeficiency viruses. The antibodies are directed against a host cell antigen complex comprising CD4 protein in assocn. with domains from chemokine receptors and have broad neutralizing activities against primary isolates from all clades of HIV type 1 (HIV-1) and primary isolates of HIV type 2 (HIV-2) and simian immunodeficiency virus (SIV). The present invention is also directed to a method of selecting and producing such antibodies, hybridomas which secrete such antibodies, pharmaceutical compns. comprising such antibodies and methods for pre- and post-exposure prevention of immunodeficiency virus infection in primates, including humans, by such antibodies whose primary targets are CD4-expressing lymphocytes.

L17 ANSWER 29 OF 66 CA COPYRIGHT 2003 ACS
AN 128:47081 CA
TI **Humanized anti-CD4** monoclonal antibody therapy of autoimmune and inflammatory disease
AU Isaacs, J. D.; Burrows, N.; Wing, M.; Keogan, M. T.; Rebello, P. R. U. B.; Watts, R. A.; Pye, R. J.; Norris, P.; Hazelman, B. L.; Hale, G.; Waldmann, H.
CS Department of Pathology, Immunology Division, Cambridge University, Cambridge, UK
SO Clinical and Experimental Immunology (1997), 110(2), 158-166
CODEN: CEXIAL; ISSN: 0009-9104
PB Blackwell
DT Journal
LA English
AB We have investigated the biol. and therapeutic properties of a **humanized anti-CD4** MoAb, hIgG1-CD4, in patients with refractory psoriasis and rheumatoid arthritis (RA). hIgG1-CD4 is a modulating, non-depleting MoAb, which induced a first-dose reaction in most patients treated. It provided brief symptomatic relief in both conditions, and psoriasis appeared easier to control with conventional agents after MoAb therapy. At the doses used, hIgG1-CD4 did not synergize therapeutically with the panlymphocyte MoAb CAMPATH-1H (C1H) in patients with RA treated sequentially with both agents. There were no

serious adverse effects definitely attributable to therapy. Our results are compared with those of other CD4 MoAb studies, and factors influencing the outcome of therapy are discussed.

L17 ANSWER 30 OF 66 CA COPYRIGHT 2003 ACS
AN 127:230352 CA
TI Fusion proteins and protein conjugates of cell type-specific protein ligands and retrovirus surface molecule ligands for use in targetting of retroviral gene therapy vectors
IN Kingsman, Alan John; Kingsman, Susan Mary
PA Oxford Biomedica (Uk) Ltd., UK; Kingsman, Alan John; Kingsman, Susan Mary
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9732026	A1	19970904	WO 1997-GB570	19970228
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9722236	A1	19970916	AU 1997-22236	19970228
	EP 883688	A1	19981216	EP 1997-905310	19970228
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	GB 2326415	A1	19981223	GB 1998-17903	19970228
	GB 2326415	B2	20000802		
	JP 2000511401	T2	20000905	JP 1997-530724	19970228
PRAI	GB 1996-4354	A	19960229		
	WO 1997-GB570	W	19970228		

AB Adapter mols. for targeting viral particles, in particular retroviral particles, to cells are fusion proteins or chem. conjugates of cell type-sp. surface ligand and a ligand for a viral surface protein such as an envelope glycoprotein. A fusion protein of a **single chain antibody** to **CD4** and a cationic amino acid transporter peptide that is a ligand for murine ecotropic viruses was prepd. by expression of the gene. The protein can be used to target these viruses to CD4+ cells. A fusion protein of VCAM-1 and the cationic amino acid transporter peptide for targetting of retroviruses to VLA4-bearing cells is also described.

L17 ANSWER 31 OF 66 CA COPYRIGHT 2003 ACS
AN 127:204198 CA
TI A humanized form of a CD4-specific monoclonal antibody exhibits decreased antigenicity and prolonged plasma half-life in rhesus monkeys while retaining its unique biological and antiviral properties
AU Reimann, Keith A.; Lin, Wenyu; Bixler, Sarah; Browning, Beth; Ehrenfels, Barbara N.; Lucci, Jodie; Miatkowski, Konrad; Olson, Dian; Parish, Thomas H.; Rosa, Margaret D.; Oleson, Frederick B.; Hsu, Yen Ming; Padlan, Eduardo A.; Letvin, Norman L.; Burkly, Linda C.
CS Division of Viral Pathogenesis, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02215, USA
SO AIDS Research and Human Retroviruses (1997), 13(11), 933-943
CODEN: ARHRE7; ISSN: 0889-2229
PB Liebert
DT Journal
LA English
AB Certain monoclonal antibodies (MAbs) directed against CD4 can efficiently

block HIV-1 replication in vitro. To explore CD4-directed passive immunotherapy for prevention or treatment of AIDS virus infection, the authors previously examd. the biol. activity of a nondepleting CD4-specific murine MAb, mu5A8. This MAb, specific for domain 2 of CD4, blocks HIV-1 replication at a post-gp120-CD4 binding step. When administered to normal rhesus monkeys, all CD4+ target cells were coated with antibody, yet no cell clearance or measurable immunosuppression occurred. However, strong anti-mouse Ig responses rapidly developed in all monkeys. Here, the authors report a successfully humanized form of mu5A8 (hu5A8) that retains binding to both human and monkey CD4 and anti-AIDS virus activity. When administered i.v. to normal rhesus monkeys, hu5A8 bound to all target CD4+ cells without depletion and showed a longer plasma half-life than mu5A8. Nevertheless, an anti-hu5A8 response directed predominantly against V region determinants did eventually appear within 2-4 wk in most animals. However, when hu5A8 was administered to rhesus monkeys chronically infected with the simian immunodeficiency virus of macaques, anti-hu5A8 antibodies were not detected. Repeated administration of hu5A8 in these animals resulted in sustained plasma levels and **CD4**+ cell coating with **humanized antibody** for 6 wk. These studies demonstrate the feasibility of chronic administration of CD4-specific MAb as a potential means of treating or preventing HIV-1 infection.

L17 ANSWER 32 OF 66 CA COPYRIGHT 2003 ACS
AN 127:204102 CA
TI Differential functional effects of a **humanized anti-CD4** antibody on resting and activated human T cells
AU Brett, S. J.; Rowan, W.; Smith, M.; Bartholomew, M.; Tite, J. P.
CS Immuno. Unit, Glaxo-Wellcome Med. Res. Cent., Stevenage, UK
SO Immunology (1997), 91(3), 346-353
CODEN: IMMUAM; ISSN: 0019-2805
PB Blackwell
DT Journal
LA English
AB A fully humanized IgG1 anti-CD4 monoclonal antibody is currently being evaluated in phase I/II clin. trials for rheumatoid arthritis. To understand the mode of action of this antibody in vivo, we have carried out a detailed functional anal. in vitro of the effects of this antibody on T-cell activation. The anti-CD4 antibody was found to inhibit both antigen-specific responses involving recognition of human leukocyte antigen (HLA) class II and processed antigenic peptides as well as non-class II dependent responses via anti-CD3 antibodies. The antibody did not cause total blockade of T-cell proliferation, but rather induced a shift in the dose-response curve, decreasing the sensitivity of cells to antigen or anti-CD3-mediated stimulation. The antibody appears to allow at least a partial early signal into the T cell as it does not inhibit the increase in tyrosine phosphorylation induced by anti-CD3 antibodies. A comparison of the intact antibody with that of either the F(ab')2 fragment or an engineered non-Fc receptor (FcR) binding from revealed that the intact antibody was the most effective at inhibiting proliferation of resting peripheral blood CD4+ T cells. However, this difference was only apparent when excess antibody was removed from culture prior to antigen or anti-CD3 mediated stimulation. The intact antibody induced both CD4 down-modulation and increases in CD4-assocd. tyrosine phosphorylation of resting CD4+ T cells, which were not seen with the non-FcR binding versions, which may account for the enhanced potency of the intact antibody at inhibiting T-cell activation. Interestingly, the anti-CD4 antibody induced a differential effect on activated CD4+ T cell clones compared with resting CD4+ T cells with respect to degree of CD4 crosslinking required to induce functional effects in the T cell. Both intact and non-FcR binding antibodies were equally effective at inhibiting T-cell proliferation of activated T-cell clones. In addn. CD4 down-modulation and increased CD4-assocd. tyrosine phosphorylation were obsd. with T-cell clones in the absence of secondary crosslinking. Such

observations may be of relevance when studying the effects of the antibody at sites of inflammation, where there will be CD4+ T cells of differing activation states as well as varying nos. of FcR pos. cells.

L17 ANSWER 33 OF 66 CA COPYRIGHT 2003 ACS
AN 127:80164 CA
TI Single-chain antibodies with membrane-binding domains that mediate adhesion between cells and their use as co-stimulatory ligands
IN Ledbetter, Jeffrey A.; Hayden, Martha; Fell, Perry; Mittler, Robert; Winberg, Gosta
PA Bristol-Myers Squibb Company, USA
SO PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9720048	A2	19970605	WO 1996-US19051	19961127

W: CA, JP, MX
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRAI US 1995-7755P P 19951130

AB Single-chain antibodies (sFv mols.) with membrane-binding domains are described. These sFv mols. stimulate adhesion between CD4+ T-cells and antigen-presenting cells thereby increasing the immune response against disease. The antigen binding domain binds a leukocyte antigen and transmembrane domain is derived from a cell surface receptor, specifically a leukocyte antigen. Retrovirus expression vectors for sFv's using monoclonal antibodies to neural cell adhesion mol. L1 with the transmembrane domain of B7 or CD58 were constructed by std. methods. Expression of the constructs in animal cell lines led to surface presentation of the antibody.

L17 ANSWER 34 OF 66 CA COPYRIGHT 2003 ACS
AN 126:263167 CA
TI Recombinant anti-CD4 antibodies for human therapy
IN Hanna, Nabil; Newman, Roland A.; Reff, Mitchell E.
PA Idec Pharmaceuticals Corporation, USA
SO PCT Int. Appl., 154 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9709351	A1	19970313	WO 1996-US14324	19960905

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA

	US 6136310	A	20001024	US 1995-523894	19950906
	AU 9669162	A1	19970327	AU 1996-69162	19960905
	AU 717674	B2	20000330		
	EP 854885	A1	19980729	EP 1996-929936	19960905

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

	BR 9610404	A	19990706	BR 1996-10404	19960905
	JP 11514216	T2	19991207	JP 1996-511411	19960905
	NO 9800915	A	19980506	NO 1998-915	19980303
PRAI	US 1995-523894	A	19950906		
	US 1991-735064	B2	19910725		

US 1992-856281 B2 19920323
US 1992-912292 B1 19920710
US 1995-379072 A2 19950125
US 1995-476237 A2 19950607
WO 1996-US14324 W 19960905

AB **Chimeric antibodies** specific to human **CD4** antigen, DNA encoding, pharmaceutical compns. contg. them and use thereof as therapeutic agents are taught. These chimeric antibodies contain Old World monkey variable sequences and human const. domain sequences, preferably human .gamma. 1, .gamma. 4 or mutated forms thereof. These antibodies possess desirable therapeutic properties including low antigenicity, reduced (or absent) T cell depleting activity, good affinity to human CD4 and enhanced stability (in vivo half-life). These antibodies are useful for treating autoimmune disease such as rheumatoid arthritis and nonautoimmune disease such as leukemia, lymphoma, graft-vs.-host disease, asthma, transplant rejection, and HIV infection. SupT1 cell-derived CD4 was used as immunogen to raise anti-CD4 IgG1 CE9.1-producing immortalized B cell line from cynomolgus monkey. Macaque/human **chimeric anti-CD4** IgG4 CE9.gamma.4PE was prepd. by genetic engineering.

L17 ANSWER 35 OF 66 CA COPYRIGHT 2003 ACS
AN 126:142902 CA
TI **Chimeric anti-CD4** antibody as a potential therapeutic agent for rheumatoid arthritis
AU Moreland, Larry W.; Koopman, William J.
CS University Alabama, Birmingham, AL, USA
SO Novel Therapeutic Agents for the Treatment of Autoimmune Diseases (1997), 41-53. Editor(s): Strand, Vibeke; Scott, David L.; Simon, Lee S. Publisher: Dekker, New York, N. Y.
CODEN: 63VZA5
DT Conference; General Review
LA English
AB A review with .apprx.31 refs.

L17 ANSWER 36 OF 66 CA COPYRIGHT 2003 ACS
AN 124:172949 CA
TI Double-blind, placebo-controlled multicenter trial using chimeric monoclonal anti-CD4 antibody, cM-T412, in rheumatoid arthritis patients receiving concomitant methotrexate
AU Moreland, Larry W.; Pratt, Parks W.; Mayes, Maureen D.; Postlethwaite, Arnold; Weisman, Michael H.; Schnitzer, Thomas; Lightfoot, Robert; Calabrese, Leonard; Zelinger, David J.; et al.
CS University Alabama, Birmingham, AL, 35294, USA
SO Arthritis & Rheumatism (1995), 38(11), 1581-8
CODEN: ARHEAW; ISSN: 0004-3591
PB Lippincott-Raven
DT Journal
LA English
AB The objective was to evaluate the clin. response to and safety of single and repeat doses of a **chimeric anti-CD4** monoclonal antibody, cM-T412, in patients with rheumatoid arthritis (RA) concomitantly treated with a stable regimen of low-dose methotrexate. Sixty-four patients with refractory RA, who were already receiving stable doses of methotrexate, were randomized into a multicenter, double-blind, placebo-controlled trial to receive 3 monthly treatments with either a placebo, or 5, 10, or 50 mg cM-T412, given i.v. Using .gtoreq.50% improvement in swollen joint counts as a criterion for clin. response, 13%, 13%, 18%, and 13% of patients receiving 50, 10, or 5 mg cM-T412, or the placebo, resp., exhibited a clin. response at 3 mo of therapy. Using .gtoreq.50% improvement in tender joint counts as a measure of clin. efficacy at 3 mo, 19%, 13%, 12%, and 6% of patients receiving 50, 10, or 5 mg cM-T412, or the placebo, resp., exhibited a clin. response. "Flu-like" symptoms (fever, chills, rigor) within 24 h of the infusion occurred more

frequently in the groups receiving 50-mg (29%) and 10-mg (31%) doses of cM-T412 than those receiving 5 mg cM-T412 (12%) or the placebo (13%). Significant CD4+ T cell depletion occurred in the 50-mg group (mean of 353 CD4+ T cells/mm3 at 6 mo vs. 856 CD4+ T cells/mm3 at baseline). All patients were followed up for 12 mo after the final treatment; no opportunistic infections complications occurred. Treatment with cM-T412 in this cohort of RA patients who were also taking methotrexate was not assocd. with clin. efficacy or enhanced toxicity from infectious complications, despite significant peripheral CD4+ T cell depletion.

L17 ANSWER 37 OF 66 CA COPYRIGHT 2003 ACS
AN 124:143123 CA
TI Treatment of cutaneous T-cell lymphoma with **chimeric anti-CD4** monoclonal antibody
AU Knox, Susan; Hoppe, Richard T.; Maloney, David; Gibbs, Iris; Fowler, Sherry; Marquez, Carol; Cornbleet, P. JoAnne; Levy, Ronald
CS Department Radiation Oncology, Stanford University School Medicine, Stanford, CA, USA
SO Blood (1996), 87(3), 893-9
CODEN: BLOOAW; ISSN: 0006-4971
PB Saunders
DT Journal
LA English
AB **Chimeric anti-CD4** monoclonal antibody was administered i.v. as a single dose to eight patients with mycosis fungoides. The dose was escalated throughout the study between patient groups, and individual patients received 50, 100, or 200 mg per dose. Seven of eight patients responded to treatment with an av. freedom from progression of 25 wk (range, 6 to 52 wk). The treatment was well tolerated, and there was no clin. evidence of immunosuppression. Following treatment, there was significant suppression of peripheral blood CD4 counts in all patients for 1 to 22+ weeks. Only one patient made a very low titer human antichimeric antibody response. All but two patients made primary antibody and T-cell proliferative responses to a foreign antigen administered 24 h after antibody infusion. However, there was generally marked, but temporary suppression of T-cell proliferative responses in vitro to phytohemagglutinin (PHA), tetanus toxoid, and normal donor lymphocytes. We conclude that at the dose levels studied, this antibody (1) had clin. efficacy against mycosis fungoides; (2) was well tolerated; (3) had a low level of immunogenicity; (4) decreased T-cell proliferative responses in vitro, and (5) did not induce tolerance to a foreign antigen.

L17 ANSWER 38 OF 66 CA COPYRIGHT 2003 ACS
AN 124:84336 CA
TI Reduction of synovial inflammation after anti-CD4 monoclonal antibody treatment in early rheumatoid arthritis
AU Tak, Paul P.; Van der Lubbe, Peter A.; Cauli, Alberto; Daha, Mohamed R.; Smeets, Tom J. M.; Kluin, Philip M.; Meinders, A. Edo; Yanni, Ghada; Panayi, Gabriel S.; Breedveld, Ferdinand C.
CS Department General Internal Medicine, University Hospital Leiden, Leiden, 2300 RC, Neth.
SO Arthritis & Rheumatism (1995), 38(10), 1457-65
CODEN: ARHEAW; ISSN: 0004-3591
PB Lippincott-Raven
DT Journal
LA English
AB The authors studied the effect of **chimeric anti-CD4** monoclonal antibody (MAb) therapy on synovial inflammation, in order to interpret the clin. experience with anti-CD4 treatment. The immunohistol. features of synovial biopsy specimens before and 4 wk after anti-CD4 MAb (cM-T412) therapy were studied in patients with rheumatoid arthritis. The patients received i.v. doses of either placebo (n = 1) or 10 mg (n = 4), 25 mg (n = 2), or 50 mg (n = 1) of cM-T412 daily for 5

consecutive days. Although the patients did not experience clin. improvement, significant decreases in the no. of circulating CD4+ cells, the degree of synovial inflammatory infiltration, and the mean scores for expression of adhesion mols. were found in the 7 patients 4 wk after receiving cM-T412. The scores for infiltration with CD4+ and other inflammatory cells were particularly reduced following treatment with either 25 mg or 50 mg cM-T412. Cytokines, such as interleukin-1.beta. and tumor necrosis factor .alpha., could still be detected in the synovial tissue after treatment. The decline in the nos. of inflammatory cells and adhesion mols. in synovial tissue after CD4+ cell depletion supports the view that CD4+ T cells orchestrate local cellular infiltration. The lack of clin. effect of anti-CD4 therapy might be explained by an insufficient decrease in the no. of synovial CD4+ cells and by the persistence of cytokines. Detn. of whether more adequate dosing would lead to a clin. improvement must await further study.

L17 ANSWER 39 OF 66 CA COPYRIGHT 2003 ACS
AN 123:336966 CA
TI Therapeutic use of a mouse/human chimeric CD4 antibody in rheumatoid arthritis
AU Dalesandro, Margaret R.; Kinney, Cheryl S.; Ghrayeb, John
CS Pharmaceutical Research, Centocor, Inc., Malvern, PA, 19355, USA
SO Methods (San Diego) (1995), 8(2), 157-65
CODEN: MTHDE9; ISSN: 1046-2023
PB Academic
DT Journal
LA English
AB Chimeric mAbs may be substituted for their murine equiv. when used in therapy to minimize the immune response directed against species-specific antigenic determinants. Open-labeled and placebo-controlled trials of the mouse/human chimeric CD4 mAb, cM-T412, were conducted in patients with rheumatoid arthritis refractory to treatment with disease-modifying anti-rheumatic drugs. The treatment was safe and well-tolerated. Doses above 10 mg caused an immediate depletion of 50-70% of circulating CD4+ lymphocytes lasting longer than was obsd. in trials using the murine parental antibody and possibly due to enhanced mediation of ADCC by the chimeric mAb. Depletion of circulating CD4+ cells did not correlate with clin. efficacy. Despite the depletion of CD4+ cells, cM-T412 therapy did not increase the incidence of opportunistic infection. Patients remained immunocompetent and 20-40% mounted an anti-chimeric antibody response. Infusion-related adverse events included fever, chills, nausea, headache, and transient hypotension. These symptoms generally correlated with an increase in serum levels of IL-6. In nonblinded studies, cM-T412 significantly decreased swollen joints in 57% of patients in one trial and reduced Ritchie articular index by .gtoreq.20% in 67% of patients in a second trial. Results of double-blind studies were mixed; some showed no significant improvement in the clin. parameters measured. The exception was a controlled trial in which patients received five consecutive 50-mg doses. This regimen resulted in high serum levels of free cM-T412 leading to the coating and depletion of synovial as well as peripheral CD4+ cells. Pos. correlation was obsd. between clin. efficacy and the proportion of cM-T412-coated synovial CD4+ cells, in contrast with the lack of correlation between clin. efficacy and depletion of circulating CD4+ lymphocytes.

L17 ANSWER 40 OF 66 CA COPYRIGHT 2003 ACS
AN 122:312621 CA
TI Functional analysis of the effects of a fully **humanized anti-CD4** antibody on resting and activated human T cells
AU Bartholomew, M.; Brett, S.; Barber, K.; Rossman, C.; Crowe, S.; Tite, J.
CS Biology Division, Wellcome Res. Lab., Kent, UK
SO Immunology (1995), 85(1), 41-8
CODEN: IMMUAM; ISSN: 0019-2805
PB Blackwell

DT Journal
LA English
AB A fully **humanized anti-CD4** antibody was studied for its effects on resting and activated CD4 T cells. Whereas the antibody was poorly lytic, it induced dramatic down-modulation of CD4 expression on both types of cell. In order to down-modulate CD4 on resting, normal CD4 T cells there was an abs. requirement for FcR-mediated crosslinking of the anti-CD4 antibody, and only CD4 levels were affected. When activated cloned T-cell lines were studied there was no requirement for crosslinking and several other cell surface markers were also affected. Although the total cellular CD4 was reduced in the down-modulated cells, as judged by Western blot anal., that CD4 which remained was assocd. with p56lck. The results are discussed in relation to the potential use of **humanized anti-CD4** antibodies in the therapy of autoimmune disease and the choice of antibody isotype for such a therapeutic antibody.

L17 ANSWER 41 OF 66 CA COPYRIGHT 2003 ACS
AN 121:298987 CA
TI Targeting of human immunodeficiency virus-infected cells by CD8+ T lymphocytes armed with universal T-cell receptors
AU Roberts, Margo R.; Qin, Lu; Zhang, Dezhen; Smith, Douglas H.; Tran, Annie-Chen; Dull, Thomas J.; Groopman, Jerome E.; Capon, Daniel J.; Byrn, Randal A.; Finer, Mitchell H.
CS Cell Genesys Inc., Foster City, CA, 94404, USA
SO Blood (1994), 84(9), 2878-89
CODEN: BLOOAW; ISSN: 0006-4971
PB Saunders
DT Journal
LA English
AB We have developed an immunotherapeutic approach with potential application in the treatment of viral and malignant disease. We show that primary CD8+ T cells isolated from peripheral blood can be genetically modified by retroviral transduction to express high levels of universal (major histocompatibility complex-unrestricted) chimeric T-cell receptors (URs) specific for human immunodeficiency virus (HIV) antigens. Two classes of HIV-specific URs in which the antigen-binding domain is comprised of either **CD4** or a **single-chain antibody** are capable of activating a no. of T-cell effector functions in response to target cells, including cytolysis, in a highly sensitive and specific manner. Importantly, we have addressed a no. of issues which, although particularly relevant to the clin. application of this approach in the treatment of HIV infection, may also impact on the potential of UR immunotherapy for other disease targets. The UR immunotherapeutic system is particularly suited for evaluation in the clin. setting.

L17 ANSWER 42 OF 66 CA COPYRIGHT 2003 ACS
AN 121:228009 CA
TI The epigenetics of multiple sclerosis: clues to etiology and a rationale for immune therapy
AU Steinman, Lawrence; Miller, Ariel; Bernard, Claude C. A.; Oksenberg, Jorge R.
CS Dep. Neurology and Neurolog. Sci., Stanford Univ., Stanford, CA, 94305, USA
SO Annual Review of Neuroscience (1994), 17, 247-65
CODEN: ARNSD5; ISSN: 0147-006X
DT Journal; General Review
LA English
AB A review, with 84 refs., on the significant advances made in the past few years, aimed at defining the nature of the immune response within the multiple sclerosis (MS) lesion. The following topics were discussed: studies on T cell receptor (TCR) rearrangements in the MS lesion; the immune response to myelin basic protein in MS; the specificity and

diversity of TCR in a cellular infiltrate; HLA and TCR genes and susceptibility to MS; selective immunotherapy targeting CD4, TCR V.beta.5.2, and myelin basic protein (MBP) in initial clin. trials in MS; clin. trials with Cop-1, orally administered MBP, **chimeric anti-CD4** antibody, and V.beta.5.2 peptides.

L17 ANSWER 43 OF 66 CA COPYRIGHT 2003 ACS
AN 121:202869 CA
TI Expression and characterization of cM-T413, a **chimeric anti-CD4** antibody with in vitro immunosuppressive activity
AU Looney, James E.; Willinger, Annette; Lin, Grace; Rieber, E. Peter; Riethmuller, Gert; Ghrayeb, John
CS Department of Molecular Biology, Centocor, Inc., Malvern, PA, 19355, USA
SO Journal of Immunotherapy with Emphasis on Tumor Immunology (1994), 16(1), 36-46
CODEN: JIEIEZ; ISSN: 1067-5582
DT Journal
LA English
AB Anti-CD4 monoclonal antibodies (mAbs) have shown considerable promise in the treatment of rheumatoid arthritis, psoriasis, and allograft rejection and may have potential use in blocking HIV-1 infection. One such anti-CD4 mAb the authors have developed, chimeric M-T412 (or cM-T412), has been used in clin. trials to treat rheumatoid arthritis, generalized postular psoriasis, and other autoimmune diseases. Here the authors report the cloning and expression of a second **chimeric anti-CD4** mAb using M-T413, a murine mAb that blocks HIV-1 infection of H9 cells. The authors cloned the Ig light and heavy chain variable regions of M-T413, combined them with the human .kappa. (light chain) or G1, G2, G3, and G4 (heavy chain) const. regions in human expression vectors, and expressed these chimeric mAbs in 653 cells. Like chimeric M-T412 IgG1, the chimeric M-T413 mAbs inhibit T-cell proliferation in the mixed lymphocyte response and thus can act to suppress CD4+ T-cell response. In contrast to M-T412, however, the M-T413 chimeric mAbs have reduced activity in an antibody-dependent cell-mediated cytotoxicity (ADCC) assay using human CD4+ target and effector cells. The authors conclude that the chimeric M-T413 mAbs have potential utility in treating autoimmune disease and may be useful as prophylactics in preventing HIV-1 infection.

L17 ANSWER 44 OF 66 CA COPYRIGHT 2003 ACS
AN 121:195062 CA
TI Development of anthrax-toxin based fusion proteins for targeting of HIV-1-infected cells
AU Leppla, S. H.; Klimpel, K. R.; Arora, N.
CS Laboratory of Microbial Ecology, National Institute of Dental Research, Bethesda, MD, 20892, USA
SO Zentralblatt fuer Bakteriologie, Supplement (1994), 24(Bacterial Protein Toxins), 431-42
CODEN: ZBASE2; ISSN: 0941-018X
DT Journal
LA English
AB Cytotoxic agents having anti-tumor and anti-viral activity have previously been constructed from protein toxins such as Pseudomonas exotoxin A (PE), diphtheria toxin (DT), and plant toxins such as ricin (RT). The three-component protein toxin of Bacillus anthracis, anthrax toxin, has several unique characteristics that can be exploited to make cell-specific cytotoxins. Fusions of the lethal factor (LF) protein to the ADP-ribosylating domain of PE were shown to be efficiently internalized into cells by the action of the protective antigen (PA) protein of the toxin. It should be possible to redirect this combination to specific cells by replacing the carboxyl-terminal, receptor-binding region of PA with targeting ligands such as **CD4**, IL-2, or **single-chain antibodies**. A second way to achieve target cell

specificity uses the fact that PA must be proteolytically cleaved to be active. Replacement of the native cleavage site of PA by the consensus sequence recognized by the HIV-1 protease may make the combination of PA and LF-PE fusion specific for cells infected by HIV-1.

L17 ANSWER 45 OF 66 CA COPYRIGHT 2003 ACS
AN 121:132220 CA
TI Genetically engineered immunoglobulins
IN Zanetti, Maurizio; Billetta, Rosario
PA Regents of the University of California, USA
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9414847	A1	19940707	WO 1993-US12339	19931217

W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRAI US 1992-996675 19921224

AB This invention relates to the introduction of oligopeptide epitopes of biol. receptor, preferably herein the CD4 receptor, for expressing within the three dimensional fold of an Ig (Ig) mol., thus creating mols. useful to induce specific, biol. active anti-receptor immunity. A **chimeric Ig** contg. at least one **CD4** HIV binding domain within the 3rd complementarity-detg. region in the N-terminus variable domain is disclosed. DNA encoding the chimeric Ig mol. and vaccine contg. the chimeric Ig are also claimed.

L17 ANSWER 46 OF 66 CA COPYRIGHT 2003 ACS
AN 121:33140 CA
TI Method for making humanized antibodies
IN Carter, Paul J.; Presta, Leonard G.
PA Genentech, Inc., USA
SO PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9404679	A1	19940303	WO 1993-US7832	19930820

W: AU, CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

	US 5821337	A	19981013	US 1992-934373	19920821
	AU 9350831	A1	19940315	AU 1993-50831	19930820
PRAI	US 1992-934373	A	19920821		
	US 1991-715272	B2	19910614		
	WO 1993-US7832	W	19930820		

AB Methods for the design of humanized antibodies by modeling them on a non-human antibody to a defined antigen using consensus Ig sequences and structural models are described. The sequence of the variable domain and CDRs of the non-human antibody and a human variable domain are compared and changes made in the CDRs of the human sequence as necessary. The framework regions (FRs) of the two sequences are then compared and the human sequence modified accordingly; care is taken to ensure that the changes in the FRs affect antigen binding and that potential glycosidation sites are not altered. A mouse monoclonal antibody against the extracellular domain of p185HER-2 was used to model humanized antibodies and a series of eight variants prepd. by expression of the corresponding cDNAs in 293 cells. The antibodies behaved as homogeneous bands on gels and all showed specific binding of the p185HER-2 antigen and an antiproliferative effect although the strength of antigen binding did not

correlate with the antiproliferative effects. Binding of one of these antibodies to p185HER-2 was 250-fold stronger than for an antibody constructed by a simple exchange of CDR loops.

L17 ANSWER 47 OF 66 CA COPYRIGHT 2003 ACS
AN 120:104424 CA
TI Active immunity against the CD4 receptor by using an antibody antigenized with residues 41-55 of the first extracellular domain
AU Lanza, Paola; Billetta, Rosario; Antonenko, Svetlana; Zanetti, Maurizio
CS Dep. Med., Univ. California, San Diego, CA, 92093-0961, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1993), 90(24), 11683-7
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB Using the process of "antibody antigenization," the authors engineered two antibody mols. carrying in the third complementarity-detg. region of the heavy chain variable domain a 7-mer or a 15-mer peptide epitope of the first extracellular domain (D1) of human CD4 receptor - namely, SFLTKGPS (positions 42-49) and GSFLTKGPSKLNDRA (positions 41-55). These amino acid sequences are contained in the consensus binding site for the human immunodeficiency virus (HIV) on CD4. Both antigenized antibodies (AgAbs) bound recombinant gp120 and were recognized by a prototype monoclonal antibody to CD4 whose binding site is within amino acid residues 41-55. AgAbs were then used as immunogens in rabbits and mice to elicit a humoral response against CD4. Only the AgAb carrying the sequence 41GSFLTKGPSKLNDRA55 induced a response against CD4. The induced antibodies showed specificity for the amino acid sequence of CD4 engineered in the AgAb mol., were able to inhibit the formation of syncytia between human CD4+ T cells MOLT-3 and 8E5 (T cells that are constitutively infected with HIV), and stained human CD4+ CEM T cells. Four murine monoclonal antibodies were used to analyze the relation between syncytia inhibition and CD4 binding at the single antibody level, and indicated that recognition of native CD4 is not an abs. requirement for inhibition of syncytia. This study demonstrates that antigenized antibodies can be used as immunogens to elicit site-specific and biol. active immunity to CD4. The importance of this approach as a general way to induce anti-receptor immunity and as a possible new measure to immunointervention in HIV infection is discussed.

L17 ANSWER 48 OF 66 CA COPYRIGHT 2003 ACS
AN 119:268568 CA
TI **Chimeric anti-CD4** monoclonal antibody cross-linked by monocyte Fc.gamma. receptor mediates apoptosis of human CD4 lymphocytes
AU Choy, Ernest H. S.; Adjaye, James; Forrest, Lesley; Kingsley, Gabrielle H.; Panayi, Gabriel S.
CS United Med. Sch., Guy's Hosp., London, UK
SO European Journal of Immunology (1993), 23(10), 2676-81
CODEN: EJIMAF; ISSN: 0014-2980
DT Journal
LA English
AB Previous studies have shown that murine anti-CD4 monoclonal antibody, cross-linked by rabbit anti-mouse Ig, could mediate apoptosis of murine CD4+ lymphocytes when they were stimulated by T cell receptor antibody. In this study, the authors have shown that the murine anti-CD4 monoclonal antibody, OKT4, can induce apoptosis in human CD4+ T cells stimulated by the recall antigen tuberculin purified protein deriv. (PPD) only when cross-linked by rabbit anti-mouse Ig. The **chimeric anti -CD4** monoclonal antibody, cM-T412 whose Fc fragment is human, was able to cause apoptosis without crosslinking by a second antibody. Similarly, abolition of PPD-induced proliferation of peripheral blood mononuclear cells by cM-T412 did not require crosslinking with rabbit anti-human Ig. Inhibition of proliferation by cM-T412 could be reduced by

pre-treating monocytes with heat-aggregated human IgG. This suggested that monocyte Fc.gamma. receptors might be crosslinking the human Fc of cM-T412. Propidium iodide staining together with immunofluorescence showed that the apoptotic cells were indeed CD4+ lymphocytes. It is proposed that during treatment with cM-T412 in autoimmune diseases such as rheumatoid arthritis, cM-T412-coated CD4 T cells, when they are subsequently stimulated by the unknown arthritogenic antigen, may undergo apoptotic cell death through crosslinking of cM-T412 on Fc.gamma. receptor-pos. cells within the joint.

L17 ANSWER 49 OF 66 CA COPYRIGHT 2003 ACS
AN 119:247609 CA
TI In vivo treatment with a monoclonal **chimeric anti-CD4** antibody results in prolonged depletion of circulating CD4+ cells in chimpanzees
AU Jonker, M.; Slingerland, W.; Treacy, G.; van Eerd, P.; Pak, K. Y.; Wilson, E.; Tam, S.; Bakker, K.; Lobuglio, A. F.; et al.
CS ITRI-TNO, Malvern, PA, USA
SO Clinical and Experimental Immunology (1993), 93(3), 301-7
CODEN: CEXIAL; ISSN: 0009-9104
DT Journal
LA English
AB Chimeric M-T412 (cM-T412), an anti-CD4 antibody, was tolerated in chimpanzees at a dosage of 5 mg/kg per day for up to 7 consecutive days, or 5 mg/kg per dose, twice weekly for 4 wk. All cM-T412-treated chimpanzees showed a prolonged CD4 cell depression. Weak chimpanzee antibody responses to chimeric M-T412 were obsd. One of the chimpanzees on the biweekly dosage regimen exhibited a hypersensitivity reaction immediately after receiving its seventh dose. Following supportive treatment, the animal recovered and remained asymptomatic during the non-treatment observation period. The hypersensitivity reaction was not an unexpected response considering the animal received repeated intermittent i.v. administration of a foreign protein. This animal also showed a chimpanzee antibody response to chimeric M-T412 after the seventh dose. Chimeric M-T412 also induced an anti-cM-T412 response in some of the other animals. The level of this response was lower than the anti-mouse responses obsd. in animals treated with murine anti-CD4. Moreover, the anti-cM-T412 response was mainly directed to idiotypic determinants. The decrease in CD4+ cells obsd. for all chimeric M-T412-treated chimpanzees is an expected effect of the anti-CD4 antibody. The duration of this CD4+ cell decrease is, however, much longer than obsd. for other CD4-specific MoAbs described. No selective loss of either memory or naive CD4+ cells was obsd. after either the single, 7-day or twice-weekly treatments. The CD4+ cell depression was reversible, although individual variation in time to recovery was obsd. Therefore, cM-T412 could be a good candidate for clin. use in autoimmune conditions.

L17 ANSWER 50 OF 66 CA COPYRIGHT 2003 ACS
AN 119:223649 CA
TI Dimerization of CD4-C.kappa. chimeric molecules leads to loss of CD4 epitopes
AU Frey, Tom; Estess, Pila; Oi, Vernon T.
CS Becton Dickinson Monoclonal Cent., San Jose, CA, 95131, USA
SO Molecular Immunology (1993), 30(9), 797-804
CODEN: MOIMD5; ISSN: 0161-5890
DT Journal
LA English
AB Structural similarities between two members of the Ig superfamily were explored by making **chimeric Ig/CD4** antigen mols. A crossover in the middle of the originally proposed J.kappa. homol. unit of the first domain of the CD4 mol. was used to construct a chimeric mol. having human and mouse CD4 antigen sequence through the first 108 amino acids and murine J.kappa. and C.kappa. sequence thereafter. This mol. was expressed in the presence and absence of an Ig

heavy chain. The resulting proteins were assayed for the expression of CD4 epitopes that should be present based on epitope mapping data. Monomeric, homodimeric, and heavy chain/light chain tetrameric forms of the recombinant protein were secreted and were all detectable with anti-kappa reagents. CD4 antibodies pptd. only the form of the CD4-C.kappa. light chain protein which appears as a monomer by polyacrylamide gel electrophoresis. Neither the homodimer nor the heavy chain/light chain tetramer were detected with CD4 monoclonal antibodies. An engineered gene having this CD4 antigen first domain joined to the human IgG1 const. region, when coexpressed with a mouse lambda light chain, also failed to express detectable CD4 epitopes. The structural implications of the presence or absence of CD4 epitopes on these proteins is discussed.

L17 ANSWER 51 OF 66 CA COPYRIGHT 2003 ACS
AN 119:178915 CA
TI Combinatorial functions of two **chimeric antibodies** directed to human **CD4** and one directed to the .alpha.-chain of the human interleukin-2 receptor
AU Weissenhorn, Winfried; Scheuer, Werner; kaluza, Brigitte; Schwirzke, Marina; Reiter, Christian; Flieger, Dimitri; Lenz, Helmut; Weiss, Elisabeth H.; Rieber, Ernst Peter; et al.
CS Inst. Immunol., Univ. Muenchen, Munich, W-8000, Germany
SO Gene (1992), 121(2), 271-8
CODEN: GENED6; ISSN: 0378-1119
DT Journal
LA English
AB The general feasibility of chimerization of monoclonal antibodies (mAbs) has already been shown for a large no. of them. In order to evaluate in vitro parameters relevant to immunosuppressive therapy, the authors have chimerized and synthesized 2 anti-CD4 mAbs recognizing 2 different epitopes on the human T-lymphocyte antigen, CD4. The chimerized mAbs are produced at levels corresponding to those of the original hybridoma cell lines. With respect to activation of human complement, the individual Abs are neg.; however, when used in combination, complement activation was performed. When applied in combination, they modulated the CD4 antigen, whereas the individual mAb do not display this property. Individually they mediate an .ltoreq. 60% inhibition of the mixed lymphocyte reaction (MLR). However, by combination of an anti-CD4 mAb with one directed against the .alpha.-chain of the human interleukin-2 (IL2) receptor, nearly 100% inhibition of the MLR was achieved, even with reduced dosage of the mAbs. Apparently, the combination of an anti-CD4 mAb and an anti-IL2R.alpha. chain mAb is more effective with respect to immunosuppression than each mAb by itself.

L17 ANSWER 52 OF 66 CA COPYRIGHT 2003 ACS
AN 119:70062 CA
TI Nonhuman primate responses to murine and humanized OKT4A
AU Delmonico, Francis L.; Cosimi, A. Benedict; Kawai, Tatsuo; Cavender, Druit; Lee, Woan Hwa; Jolliffe, Linda K.; Knowles, Robert W.
CS Dep. Surg., Massachusetts Gen. Hosp., Boston, MA, 02114, USA
SO Transplantation (1993), 55(4), 722-8
CODEN: TRPLAU; ISSN: 0041-1337
DT Journal
LA English
AB A nonhuman primate anti-murine response (MAMA) has been obsd. in 17 cynomolgus renal allograft recipients of murine OKT4A. Neither cyclosporine, nor total-lymphoid irradn., nor donor bone marrow prepn. inhibited this anti-xenogeneic response. To alter the anti-murine basis of the response, a humanized chimeric OKT4A (IgG4) contg. the entire variable portion of the murine OKT4A and a humanized CDR grafted OKT4A mAb sharing only the complementarity detg. region from the murine OKT4A, were administered to 8 cynomolgus allograft recipients. MAMA was detected in each recipient. In contrast to sera from recipients of murine OKT4A, sera

from recipients of humanized OKT4A displayed no reactivity to other murine mAbs. MAMA specificity did not assay const. (C) region differences between the murine and humanized mAb; however, C region homol. in humans should preclude a human anti-mouse antibody (HAMA) to the Fc portion of a humanized mAb. Furthermore, cynomolgus recipient serum levels of the humanized OKT4A mAb were maintained (>1 .mu.g/mL) for a longer period than following treatment with murine OKT4A (murine <12 days vs. between 12 and 24 days for the humanized). If the HAMA response to humanized mAb in future clin. trials, were to be predictably anti-idiotypic, then the opportunity for treatment with sequential mAbs of differing idiotypes would be retained. Moreover, these current studies also suggest that humanized construction may influence the duration of therapeutic mAb levels. Thus, anti-idiotypic reactivity may not be as consequential to the clin. administration of humanized mAb to allograft recipients.

L17 ANSWER 53 OF 66 CA COPYRIGHT 2003 ACS
AN 118:231914 CA
TI Nonhuman primate response to murine and humanized monoclonal antibodies
AU Delmonico, F. L.; Cosimi, A. B.
CS Dep. Surg., Massachusetts Gen. Hosp., Boston, MA, 02114, USA
SO Transplantation Proceedings (1993), 24(2, Suppl. 1), 65-7
CODEN: TRPPA8; ISSN: 0041-1345
DT Journal
LA English
AB In most rodent exptl. models, the administration of a xenogeneic monoclonal antibody (MAb) induces a pattern of anti-MAb reactivity similar to that obsd. in large mammalian recipients. Inhibition of this response has been accomplished by the administration of MAb directed against the CD4 population of mouse T cells (L3T4). Rat anti-L3T4 MAb inhibited the murine response to this MAb. Moreover, anti-CD4 MAbs inhibited anti-MAb reactivity to other MAbs given simultaneously. Despite these encouraging small-animal observations, monkey antimouse antibodies (MAMA) were detected routinely in cynomolgus recipients of murine OKT4A, even when concomitant immunosuppression was given. Thus, in contrast to the effects of the anti-CD4 MAb cited above, murine OKT4A (as given to nonhuman primates in these expts.) did not induce a tolerance to itself.

L17 ANSWER 54 OF 66 CA COPYRIGHT 2003 ACS
AN 118:99996 CA
TI "Primatization" of recombinant antibodies for immunotherapy of human diseases: a macaque/human **chimeric antibody** against human **CD4**
AU Newman, Roland; Alberts, James; Anderson, Darrell; Carner, Kristin; Heard, Cheryl; Norton, Frank; Raab, Ron; Reff, Mitchell; Shuey, Steve; Hanna, Nabil
CS IDEC Pharm. Corp., La Jolla, CA, 92037, USA
SO Bio/Technology (1992), 10(11), 1455-60
CODEN: BTCHDA; ISSN: 0733-222X
DT Journal
LA English
AB Ig variable region genes from non-human primates, cynomolgus macaques, were shown to have 85-98% homol. with human Ig sequences and yet macaques are phylogenetically distant enough to respond against conserved human antigens. Immunoglobulin genes were isolated from monkeys immunized with human CD4 antigen and a human/monkey **chimeric anti-CD4** antibody with 91-92% homol. to human Ig framework regions was cloned and expressed. The antibody has an apparent affinity of 3.2 .times. 10-11M and exhibits potent immunosuppressive properties in vitro.

L17 ANSWER 55 OF 66 CA COPYRIGHT 2003 ACS
AN 118:79199 CA
TI From antilymphocyte serum to therapeutic monoclonal antibodies: first experiences with a chimeric CD4 antibody in the treatment of autoimmune disease

AU Riethmueller, Gert; Rieber, Ernst Peter; Kiefersauer, Stefan; Prinz, Joerg; Van der Lubbe, Peter; Meiser, Bruno; Breedveld, Ferdy; Eisenburg, Josef; Krueger, Klaus; et al.
CS Inst. Immunol., Univ. Muenchen, Munich, Germany
SO Immunological Reviews (1992), 129, 81-104
CODEN: IMRED2; ISSN: 0105-2896
DT Journal
LA English
AB The clin. data on the therapeutic effects of chimeric CD4 antibody on human autoimmune disease are clearly promising though not consistent for each clin. entity tested. The big surprise so far is the paucity of side effects and the conspicuous absence of a more general immunosuppression. An unexpected and as yet unexplained finding is the selective and sustained CD4 T-cell depletion of several months duration. The proposal is made that, after an initial indiscriminate depletion of CD4 T cells, the antibody therapy triggers an active depression of autoreactive CD4 T cells allowing the preferential recovery of T lymphocytes competent for foreign antigens.

L17 ANSWER 56 OF 66 CA COPYRIGHT 2003 ACS
AN 117:149291 CA
TI Anti-CD4 antibodies blocking human immunodeficiency virus (HIV)-induced syncytia, and diagnostic and therapeutic uses thereof
IN Burkly, Linda C.; Chisholm, Patricia L.; Thomas, David W.; Rosa, Margaret D.; Rosa, Joseph J.
PA Biogen, Inc., USA
SO PCT Int. Appl., 187 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9209305	A1	19920611	WO 1991-US8843	19911127
	W: AU, CA, JP, US				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	CA 2073031	AA	19920528	CA 1991-2073031	19911127
	AU 9191543	A1	19920625	AU 1991-91543	19911127
	AU 662891	B2	19950921		
	EP 512112	A1	19921111	EP 1992-903295	19911127
	EP 512112	B1	19970528		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05505112	T2	19930805	JP 1992-503666	19911127
	AT 153536	E	19970615	AT 1992-903295	19911127
	ES 2101834	T3	19970716	ES 1992-903295	19911127
PRAI	US 1990-618542		19901127		
	WO 1991-US8843		19911127		

AB Anti-CD4 antibody homologs are provided, as are DNA sequences and recombinant DNA mols. encoding them, prophylactic, immunotherapeutic, and diagnostic compns. comprising them, and methods for preventing or treating diseases in mammals, including humans, caused by infective agents whose primary targets are CD4-pos. lymphocytes. Such diseases include AIDS, AIDS-related complex, and HIV infection. The immunogen used in the generation of monoclonal antibodies (MAbs) 1F8, 5A8, and 5F2 was CHO cells transformed with DNA encoding full-length human CD4 expressed on the cell surface. The efficacy of MAb 5A8 was comparable to that of Leu3A and OKT4A, with 50% syncytia blocking achieved at .apprx.10 ng/mL. The 5A8 MAb was able to block reproducibly the establishment of HIV infection in CD4-pos. cells; MAbs 1F8 and 5F2 also showed evidence of being able to block HIV infection. MAb 5A8 had no significant effect on indicia of immunosuppression in vivo. Use of recombinant DNA methodol. to humanize 5A8 heavy and light chains is described (DNA and amino acid sequences included).

L17 ANSWER 57 OF 66 CA COPYRIGHT 2003 ACS
AN 117:63005 CA
TI Immunosuppressants for treatment of lung diseases
IN Kay, Anthony Barry; Barnes, Neil Christopher; Cole, Peter John
PA National Heart and Lung Institute, UK
SO PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9208474	A2	19920529	WO 1991-GB2049	19911120
	WO 9208474	A3	19920625		
	W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MN, MW, NL, NO, PL, RO, SD, SE, SU, US				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	AU 9189108	A1	19920611	AU 1991-89108	19911120
PRAI	GB 1990-25154		19901120		
	GB 1990-26620		19901207		
	WO 1991-GB2049		19911120		

AB Specific pharmacol. targeting of T-lymphocytes provides a new approach to the treatment of chronic asthma (both in patients relatively sensitive and resistant to the effects of corticosteroids) and to the treatment of other lung diseases (e.g. bronchiectasis and cystic fibrosis), as well as sinusitis. Cyclosporin A (I) and other immunosuppressants (e.g. FK 506, rapamycin, **humanized anti-CD4** antibodies) with the same or similar mode or site of action are provided for the treatment of diseases characterized by airflow obstruction and/or of chronic sinusitis. Also provided is an in vitro test for prediction of clin. response to corticosteroids and immunosuppressants. Corticosteroid resistance can be identified by the in vitro test, and corticosteroid-resistant patients thus identified can be treated with I or other suitable immunosuppressant. When patients with long-standing corticosteroid-dependent asthma were treated with I, there were significant increases above placebo in both morning and evening peak expiratory flow both pre- and post-bronchodilator. Patients on I suffered significantly fewer exacerbations requiring rescue prednisolone compared to placebo.

L17 ANSWER 58 OF 66 CA COPYRIGHT 2003 ACS
AN 116:104006 CA
TI Production and comparison of anti-**CD4 chimeric antibodies** for the induction of tolerance to skin allografts in mice
AU Rashid, Asif
CS Boston Univ., Boston, MA, USA
SO (1991) 183 pp. Avail.: Univ. Microfilms Int., Order No. DA9128415
From: Diss. Abstr. Int. B 1991, 52(4), 1967
DT Dissertation
LA English
AB Unavailable

L17 ANSWER 59 OF 66 CA COPYRIGHT 2003 ACS
AN 116:56937 CA
TI Reshaping a therapeutic CD4 antibody
AU Gorman, Scott D.; Clark, Michael R.; Routledge, Edward G.; Cobbold, Stephen P.; Waldmann, Herman
CS Dep. Pathol., Univ. Cambridge, Cambridge, CB2 1QP, UK
SO Proceedings of the National Academy of Sciences of the United States of America (1991), 88(10), 4181-5
CODEN: PNASA6; ISSN: 0027-8424

DT Journal
LA English
AB An immunosuppressive rat antibody (Campath-9) against human CD4 has been reshaped for use in the management of autoimmunity and the prevention of graft rejection. Two different forms of the reshaped antibody were produced that derive their heavy chain variable region framework sequences from the human myeloma proteins KOL or NEW. When compared to chimeric form of the CD4 antibody, the avidity of the KOL-based reshaped antibody was only slightly reduced, whereas that of the NEW-based reshaped antibody was very poor. The successful reshaping to the KOL-based framework was by a procedure involving the grafting of human framework sequences onto the cloned rodent variable region by in vitro mutagenesis.

L17 ANSWER 60 OF 66 CA COPYRIGHT 2003 ACS
AN 116:39674 CA
TI CD4-specific recombinant antibody
IN Jolliffe, Linda Kay; Zivin, Robert Allan; Pulito, Virginia Lee; Adair, John Robert; Athwal, Diljeet Singh
PA Ortho Pharmaceutical Corp., USA
SO PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9109966	A1	19910711	WO 1990-GB2015	19901221
	W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, GR, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU, US				
	RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	CA 2046904	AA	19910622	CA 1990-2046904	19901221
	CA 2050479	AA	19910622	CA 1990-2050479	19901221
	CA 2050479	C	19970325		
	AU 9170486	A1	19910724	AU 1991-70486	19901221
	AU 631481	B2	19921126		
	EP 460178	A1	19911211	EP 1991-901835	19901221
	EP 460178	B1	19971015		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	HU 58372	A2	19920228	HU 1991-2734	19901221
	HU 215383	B	20000328		
	HU 58824	A2	19920330	HU 1991-2752	19901221
	HU 60786	A2	19921028	HU 1991-2751	19901221
	JP 05500312	T2	19930128	JP 1991-502107	19901221
	GB 2268744	A1	19940119	GB 1993-18911	19901221
	GB 2268744	B2	19940511		
	GB 2268745	A1	19940119	GB 1993-18912	19901221
	GB 2268745	B2	19940511		
	EP 620276	A1	19941019	EP 1994-104042	19901221
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	EP 626390	A1	19941130	EP 1994-202090	19901221
	EP 626390	B1	20011114		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	ES 2074701	T3	19950916	ES 1991-901559	19901221
	AT 129017	E	19951015	AT 1991-901433	19901221
	ES 2079638	T3	19960116	ES 1991-901433	19901221
	AT 159299	E	19971115	AT 1991-901835	19901221
	ES 2112270	T3	19980401	ES 1991-901835	19901221
	RU 2112037	C1	19980527	RU 1990-5001870	19901221
	JP 11243955	A2	19990914	JP 1997-353861	19901221
	RO 114980	B1	19990930	RO 1990-148283	19901221
	HU 217693	B	20000328	HU 1990-2752	19901221
	AT 208794	E	20011115	AT 1994-202090	19901221
	ES 2165864	T3	20020401	ES 1994-202090	19901221

	CA 2037607	AA	19920907	CA 1991-2037607	19910306
	CA 2129219	C	19981222	CA 1991-2129219	19910306
	NO 9103271	A	19910820	NO 1991-3271	19910820
	US 5929212	A	19990727	US 1993-116247	19930903
	AU 9464612	A1	19941222	AU 1994-64612	19940608
	AU 664801	B2	19951130		
	US 5859205	A	19990112	US 1994-303569	19940907
	FI 9900875	A	19990419	FI 1999-875	19990419
PRAI	GB 1989-28874	A	19891221		
	EP 1991-901433	A3	19901221		
	JP 1991-501864	A3	19901221		
	WO 1990-GB2015	A	19901221		
	CA 1991-2037607	A3	19910306		
	GB 1991-17611	A3	19910815		
	GB 1991-17612	A3	19910815		
	FI 1991-3932	A3	19910820		
	US 1991-743329	B1	19910917		

AB A complementarity-detg. region (CDR)-grafted antibody has .gtoreq.1 chain wherein the framework regions are predominantly derived from a 1st antibody (acceptor) and .gtoreq.1 CDR is derived from 2nd antibody (donor), the CDR-grafted antibody being capable of binding to the CD4 antigen. In chimeric antibodies, certain amino acid residues in the framework regions derived from human antibodies are converted to correspond to the equiv. amino acid in the donor antibody. Cloning and prodn. of chimeric OKT4A monoclonal antibodies are presented. The chimeric OKT4A antibodies bound CD4 and inhibited T-cell proliferation.

L17 ANSWER 61 OF 66 CA COPYRIGHT 2003 ACS
AN 116:5190 CA
TI Humanised antibodies
IN Adair, John Robert; Athwal, Diljeet Singh; Emtage, John Spencer
PA Celltech Ltd., UK
SO PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9109967	A1	19910711	WO 1990-GB2017	19901221
	W: AT, AU, BB, BG, BR, CH, DE, DK, FI, GB, GR, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU, US				
	RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	CA 2046904	AA	19910622	CA 1990-2046904	19901221
	CA 2050479	AA	19910622	CA 1990-2050479	19901221
	CA 2050479	C	19970325		
	AU 9169740	A1	19910724	AU 1991-69740	19901221
	AU 646009	B2	19940203		
	EP 460167	A1	19911211	EP 1991-901433	19901221
	EP 460167	B1	19951011		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	BR 9007197	A	19920128	BR 1990-7197	19901221
	HU 58372	A2	19920228	HU 1991-2734	19901221
	HU 215383	B	20000328		
	HU 58824	A2	19920330	HU 1991-2752	19901221
	JP 04505398	T2	19920924	JP 1991-501864	19901221
	HU 60786	A2	19921028	HU 1991-2751	19901221
	GB 2268744	A1	19940119	GB 1993-18911	19901221
	GB 2268744	B2	19940511		
	GB 2268745	A1	19940119	GB 1993-18912	19901221
	GB 2268745	B2	19940511		
	EP 620276	A1	19941019	EP 1994-104042	19901221
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				

EP 626390	A1	19941130	EP 1994-202090	19901221
EP 626390	B1	20011114		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
ES 2074701	T3	19950916	ES 1991-901559	19901221
AT 129017	E	19951015	AT 1991-901433	19901221
ES 2079638	T3	19960116	ES 1991-901433	19901221
AT 159299	E	19971115	AT 1991-901835	19901221
ES 2112270	T3	19980401	ES 1991-901835	19901221
RO 114298	B1	19990330	RO 1990-148282	19901221
JP 11243955	A2	19990914	JP 1997-353861	19901221
AT 208794	E	20011115	AT 1994-202090	19901221
ES 2165864	T3	20020401	ES 1994-202090	19901221
CA 2037607	AA	19920907	CA 1991-2037607	19910306
CA 2129219	C	19981222	CA 1991-2129219	19910306
WO 9201059	A1	19920123	WO 1991-GB1108	19910705
W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MN, MW, NL, NO, PL, RO, SD, SE, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
AU 9182005	A1	19920204	AU 1991-82005	19910705
AU 651984	B2	19940811		
EP 491031	A1	19920624	EP 1991-912863	19910705
EP 491031	B1	19960501		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05502587	T2	19930513	JP 1991-512027	19910705
AT 137534	E	19960515	AT 1991-912863	19910705
GB 2246570	A1	19920205	GB 1991-17612	19910815
GB 2246570	B2	19940511		
NO 9103228	A	19911021	NO 1991-3228	19910819
CA 2076540	AA	19920622	CA 1991-2076540	19911220
WO 9211383	A1	19920709	WO 1991-GB2300	19911220
W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, SD, SE, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG				
AU 9191084	A1	19920722	AU 1991-91084	19911220
AU 657937	B2	19950330		
NL 9120013	A	19921102	NL 1991-20013	19911220
EP 516785	A1	19921209	EP 1992-901287	19911220
EP 516785	B1	19960221		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
DE 4193302	T	19930218	DE 1991-4193302	19911220
DE 4193302	C2	20000824		
BR 9106232	A	19930330	BR 1991-6232	19911220
HU 62661	A2	19930528	HU 1992-2605	19911220
JP 05507418	T2	19931028	JP 1992-501467	19911220
JP 3145401	B2	20010312		
EP 626389	A1	19941130	EP 1994-201456	19911220
EP 626389	B1	20021204		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
AT 134387	E	19960315	AT 1992-901287	19911220
ES 2084338	T3	19960501	ES 1992-901287	19911220
JP 10136986	A2	19980526	JP 1997-8037	19911220
EP 927758	A2	19990707	EP 1998-202522	19911220
EP 927758	A3	20010221		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC				
JP 2001114697	A2	20010424	JP 2000-270382	19911220
AT 228853	E	20021215	AT 1994-201456	19911220
ZA 9110129	A	19930623	ZA 1991-10129	19911223
GB 2251859	A1	19920722	GB 1992-4803	19920305
GB 2251859	B2	19950111		
NO 9203231	A	19921020	NO 1992-3231	19920818
FI 9203737	A	19920820	FI 1992-3737	19920820
GB 2257145	A1	19930106	GB 1992-17880	19920821

	GB 2257145	B2	19950614		
	US 5929212	A	19990727	US 1993-116247	19930903
	GB 2276169	A1	19940921	GB 1994-8203	19940425
	AU 9464612	A1	19941222	AU 1994-64612	19940608
	AU 664801	B2	19951130		
	GB 2279077	A1	19941221	GB 1994-15380	19940729
	GB 2279077	B2	19950614		
	US 5859205	A	19990112	US 1994-303569	19940907
	AU 9477723	A1	19950309	AU 1994-77723	19941109
	AU 669083	B2	19960523		
	US 5994510	A	19991130	US 1995-456418	19950601
	NO 9805468	A	19911021	NO 1998-5468	19981123
	NO 2001002882	A	19921020	NO 2001-2882	20010611
PRAI	GB 1989-28874	A	19891221		
	GB 1990-14932	A	19900705		
	EP 1991-901433	A3	19901221		
	JP 1991-501864	A3	19901221		
	WO 1990-GB2017	A	19901221		
	CA 1991-2037607	A3	19910306		
	GB 1991-9645	A	19910503		
	WO 1991-GB1108	A	19910705		
	GB 1991-17611	A3	19910815		
	GB 1991-17612	A3	19910815		
	US 1991-743329	B1	19910917		
	EP 1992-901287	A3	19911220		
	EP 1994-201456	A3	19911220		
	JP 1992-501467	A3	19911220		
	WO 1991-GB2300	A	19911220		
	GB 1992-4803	A3	19920305		
	GB 1992-17880	A3	19920821		
	US 1995-373882	B1	19950117		

AB CDR-grafted antibody (CDR = complementarity-detn. region) heavy and high chains comprise acceptor framework and donor antigen binding regions, the heavy chains comprising donor residues at at least one of positions (6.23) and/or (24, 48) and/or (49, 71) and/or (73, 75) and/or (76) and/or (78) and (88) and/or (91). The CDR-grafted light chains comprise donor residues at at least one of positions (1) and/or (3) and (46) and/or (47) or at at least one of positions (46, 48, 58) and (71). The CDR-grafted antibodies are preferably humanized antibodies, having non human, e.g. rodent, donor and human acceptor frameworks, and may be used for in vivo therapy and diagnosis. A generally applicable protocol is disclosed for obtaining CDR-grafted antibodies. Thus, a fully chimeric OKT3 antibody was produced which was fully capable of binding to CD3-pos. cells and blocking the binding of murine OKT3 to these cells. Construction of chimeric genes and chimeric expression vectors, and expression in mammalian cells of the chimeric genes, are described. It was demonstrated for OKT3 that to transfer antigen binding ability to the humanized antibody, mouse residues outside the CDR regions defined by the Kabat hypervariability or structural loop choices are required for both the light and heavy chains. Fewer extra residues are needed for the light chain, possibly due to the higher initial homol. between the mouse and human .kappa. variable regions. CDR graft sequences are included for the OKT3 grafted antibody. CDR-grafted antibodies specific for e.g. CD4 T-cell receptor, for mucin, for intercellular adhesion mol.-1, and for tumor necrosis factor-.alpha. are described.

L17 ANSWER 62 OF 66 CA COPYRIGHT 2003 ACS
AN 115:133999 CA
TI **Chimeric immunoglobulin** for **CD4** receptors
IN Ghrayeb, John; Knight, David M.; Looney, James E.
PA Centocor, Inc., USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent

LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9110722	A2	19910725	WO 1990-US7671	19901227
	WO 9110722	A3	19910905		
	W: CA, JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
	CA 2070182	AA	19910628	CA 1990-2070182	19901227
	EP 511308	A1	19921104	EP 1991-903980	19901227
	EP 511308	B1	19960925		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05502586	T2	19930513	JP 1991-504098	19901227
	AT 143377	E	19961015	AT 1991-903980	19901227
	US 2001051709	A1	20011213	US 2001-896050	20010629
PRAI	US 1989-457389	A2	19891227		
	WO 1990-US7671	W	19901227		
	US 1992-867100	B1	19920625		

AB A chimeric antibody is provided comprising a variable or antigen-binding region of nonhuman origin specific for the CD4 receptor and a const. region of human origin. The antibody is useful as a therapeutic agent for autoimmune disorders. Thus light and heavy chain variable region genes were cloned from murine hybridoma M-T412 [producing anti-CD4 monoclonal antibody (MAb)]. The cloned genes were joined to human .kappa. and G1 const. region genes in expression vectors. The chimeric antibody was purified from tissue culture supernatant of cell line JL3A3. When a preferred **chimeric anti-CD4** MAb (cM-T412) was administered to chimpanzees, the antibody was well tolerated and circulating CD4 cell no. was markedly decreased from the 1st dose through 2-3 wk after the last dose. The CD4-pos. cells increased in no. 3-4 wk post dose, but remained depressed in treated animals relative to control animals for 3-4 mo. Administration of a preferred **chimeric anti-CD4** MAb to human patients with refractory rheumatoid arthritis resulted in significant improvement of symptoms.

L17 ANSWER 63 OF 66 CA COPYRIGHT 2003 ACS
AN 115:90553 CA
TI Genetically engineered immunoglobulins
IN Zanetti, Maurizio; Sollazzo, Maurizio
PA University of California, Berkeley, USA
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9009804	A1	19900907	WO 1990-US1010	19900223
	W: CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
	CA 2047244	AA	19900825	CA 1990-2047244	19900223
	EP 460076	A1	19911211	EP 1990-904172	19900223
	EP 460076	B1	19951129		
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
	JP 04503605	T2	19920702	JP 1990-504424	19900223
	AT 130765	E	19951215	AT 1990-904172	19900223
	ES 2082850	T3	19960401	ES 1990-904172	19900223
	JP 2001190295	A2	20010717	JP 2000-370024	19900223
	US 5508386	A	19960416	US 1994-357495	19941216
	US 5583202	A	19961210	US 1994-357452	19941216
	US 5658762	A	19970819	US 1995-476914	19950606
PRAI	US 1989-316144	A	19890224		
	JP 1990-504424	A3	19900223		
	WO 1990-US1010	W	19900223		

US 1992-947415 B1 19920918
US 1992-947521 B1 19920918
US 1994-357452 A3 19941216

AB The title Igs contain .gtoreq.1 heterologous epitope within the N-terminal variable, while retaining the functionality of the C-terminus heavy chain const. region specific for a particular cell or receptor, and having specific epitope reactivity. Three copies of the tetrapeptide NANP, occurring in the Plasmodium falciparum circumsporozoite protein, were inserted into the VH62k coding region of plasmid pH62k (prepn. described), encoding the VH gene of a murine monoclonal antibody to thyroglobulin. The EcoR1 restriction fragment was then cloned into plasmid pNY1 to give the expression vector pNY1NANP. The recombinant antibody y1NANP was used to induce anti-NANP antibodies in mice and rabbits.

L17 ANSWER 64 OF 66 CA COPYRIGHT 2003 ACS
AN 113:229546 CA
TI Chimeric and mosaic antibodies to Leu 3a antigen
IN Hinton, Robert; Oi, Vernon T.
PA Becton, Dickinson and Co., USA
SO Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 365209	A2	19900425	EP 1989-310415	19891011
	EP 365209	A3	19900725		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 02238883	A2	19900921	JP 1989-270152	19891017
PRAI	US 1988-260558		19881017		

AB Genes for chimeric and mosaic mouse/human antibodies to CD4 antigen Leu 3a are prepd. The antibodies are of use in the treatment of CD4+-related immune dysfunction. The genes were constructed by std. methods.

L17 ANSWER 65 OF 66 CA COPYRIGHT 2003 ACS
AN 113:108922 CA
TI Expression and characterization of human CD4: immunoglobulin fusion proteins
AU Zettlmeissl, Gerd; Gregersen, Jens Peter; Duport, Jean Michel; Mehdi, Sabine; Reiner, Goetz; Seed, Brian
CS Res. Lab., Behringwerke A.-G., Marburg, D-3550, Germany
SO DNA and Cell Biology (1990), 9(5), 347-53
CODEN: DCEBE8; ISSN: 1044-5498
DT Journal
LA English
AB Different chimeric antibody-like mols. consisting of the four human CD4 extracellular domains (amino acids 1-369) fused to different parts of human IgG1 and IgM heavy-chain const. regions have been created and expressed in mammalian cells. For both IgG1 and IgM fusion proteins, the best expression in COS cells was obsd. for mols. lacking the CH1 domain of the heavy-chain const. region. The chimeric mols. are potent inhibitors of human immunodeficiency virus (HIV) infection and HIV-mediated cytotoxicity. A CD4:IgG1 hinge fusion protein, which was analyzed in more detail, binds efficiently to HIV gp160 and human Fc receptors and shows complement-assisted inhibition of viral propagation in culture. Half-life studies after i.v. application of the latter human fusion protein into mice and monkeys showed prolongation of serum survival compared to sol. CD4. An IgG2b murine homolog of the human CD4:IgG1 hinge fusion protein was prepd. and evaluated in mice, where it was found to be nontoxic and to have no detectable effect on the humoral response to sol. antigen.

L17 ANSWER 66 OF 66 CA COPYRIGHT 2003 ACS
AN 113:95863 CA

TI Mechanisms of anti-CD4-mediated depletion and immunotherapy. A study using a set of **chimeric anti-CD4** antibodies

AU Alters, Susan E.; Sakai, Koichiro; Steinman, Lawrence; Oi, Vernon T.
CS Sch. Med., Stanford Univ., Stanford, CA, 94305, USA

SO Journal of Immunology (1990), 144(12), 4587-92
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English

AB A family of rat-mouse chimeric anti-murine CD4 antibodies was used to study the mechanisms of anti-CD4-mediated depletion and immunotherapy. The chimeric antibodies retain identical affinity and specificity as the therapeutically effective prototype antibody, rat GK1.5, but are of different mouse isotypes. GK1.5.gamma.1, GK1.5.gamma.2a, and GK1.5.gamma.2b are more effective at CD4+ cell depletion that rat GK1.5 when low doses of antibody are administered. Depletion of CD4+ cells in vivo is not correlated with either the ability of the antibody to mediate C-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity in vitro, implying that addnl. antibody-mediated cytotoxic mechanisms occur in vivo. The chimeric antibodies were used to investigate the mechanisms of GK1.5-mediated immunotherapy in a prototypic model of T cell-mediated autoimmunity, exptl. allergic encephalomyelitis. Mice treated with a single dose of 100 .mu.g of either GK1.5, GK1.5.gamma.1, or GK1.5.gamma.2a showed recovery within 72 h. These data suggest that anti-CD4-mediated immunotherapy of murine exptl. allergic encephalomyelitis is correlated with depletion of CD4+ cells.

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